STEP-UP to MEDICINE

6TH EDITION

Steven Agabegi
Elizabeth Agabegi

LEAD EDITORS
Mark D. Duncan
Kelley Chuang

- **GOLD STANDARD** for clerkship, shelf exam, and USMLE Step 2 review
- More than **1,000 QUICK HITS** and **CLINICAL PEARLS**
- **BOARD-STYLE QUESTIONS** with accurate and insightful explanations *(available in print and online—more than 400 questions!)*
- **FULLY UPDATED** chapters reflect current **EVIDENCE-BASED CARE**

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Prepress Vendor: Aptara, Inc.

Sixth edition

9 8 7 6 5 4 3 2 1

Printed in Mexico

Library of Congress Cataloging-in-Publication Data available upon request.

978-1-975192-74-7

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The authors and publisher would like to thank the following student reviewers who provided valuable input in revising the new edition, as well as the many student readers who have provided ongoing feedback since the book's original publication.

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PREFACE

It is hard to believe that it has been 14 years since the first edition of *Step-Up to Medicine* was published. Now in its sixth edition, the success of this book has always been linked to its in-depth, yet concise coverage of every medical topic that a student will encounter during the clinical years of medical school and corresponding NBME shelf examinations.

This sixth edition of *Step-Up to Medicine* has been extensively revised and edited based on constructive feedback from students, residents, and faculty. To this end, we recruited a stellar team of medical professionals, led by Dr. Mark Duncan and Dr. Kelley Chuang, to update every topic and enrich the content of each chapter. We would like to acknowledge and sincerely thank these physicians for offering their expertise and valuable time in this endeavor. The quality of this edition of *Step-Up to Medicine* is the result of their tireless efforts.

We hope you find this new edition of *Step-Up to Medicine* a valuable study tool during your clinical years of medical school. We welcome any feedback or suggestions you may have for future editions. Please email us at agabegs@ucmail.uc.edu.

Steve and Liz Agabegi

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Diseases of the Cardiovascular System

1

Mark Duncan

Chest Pain

A. Differential Diagnosis

1. Heart, pericardium, vascular causes
   a. Stable angina
   b. ACS—unstable angina (UA), non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI)
   c. Pericarditis
   d. Aortic dissection
2. Pulmonary: Pulmonary embolism (PE, can have pain with pulmonary infarction), pneumothorax, pleuritis (pleural pain), pneumonia, status asthmaticus
3. GI: Gastroesophageal reflux disease (GERD), diffuse esophageal spasm, peptic ulcer disease, esophageal rupture
4. Chest wall: Costochondritis, muscle strain, rib fracture, herpes zoster
5. Psychiatric: Panic attacks, anxiety, somatization
6. Cocaine/methamphetamine use can cause angina or MI

Quick HIT

If you suspect a cardiac cause of the pain, sublingual nitroglycerin is appropriate. Also give aspirin if the patient does not have a bleeding disorder.

B. Approach to Treating a Patient With Chest Pain

1. Rule out any life-threatening causes. These include ACS, aortic dissection, pericarditis with cardiac tamponade, pulmonary embolism, tension pneumothorax, and esophageal rupture
2. Assess vital signs
3. Develop a focused history
   a. Character of the pain (pressure, squeezing, tearing, sharp, stabbing, etc.)
   b. Location of pain
   c. Severity of pain
   d. Duration of pain
   e. Setting in which pain occurred (during exertion, at rest, after meal)
   f. Radiation of pain
   g. Aggravating or alleviating factors (e.g., meal, exertion, rest, respiration)
   h. *Does the patient have a cardiac history?* Ask about results of previous stress tests, echocardiograms, cardiac catheterization, or of any procedures (PCI or CABG)
   i. *If the patient has a history of angina, ask how this episode differs from previous ones (more severe? longer duration?)*
4. Perform a focused physical examination, with attention to cardiopulmonary, abdominal, and musculoskeletal examination
5. Order ancillary tests
   a. Obtain ECG in almost all cases
   b. Cardiac enzymes (e.g., troponin) depending on clinical suspicion
   c. Obtain chest x-ray (CXR) in almost all cases
   d. Under appropriate clinical setting, work up the patient for PE (see Pulmonary section)
6. Develop a diagnosis
   a. It can be difficult to distinguish between GI causes of chest pain and angina. The decision of whether to initiate a cardiac workup is dependent on a patient's overall risk of coronary artery disease (CAD) and the clinical presentation
   b. There is no fail-proof algorithm for approaching chest pain. In general, have a greater index of suspicion for ischemic causes in the elderly, diabetic populations, and those with a history of CAD (see

myocardial infarction [MI] section). Risk stratification scores can be helpful for evaluating patients in the emergency department (e.g., HEART score)

Quick HIT

If nitroglycerin relieves the pain, a cardiac cause is more likely (although nitrates also relieve pain from diffuse esophageal spasm).

Quick HIT

If chest pain is pleuritic, positional, or reproduced with chest wall palpation, a cardiac cause may be less likely.

Quick HIT

A common presentation is a patient with chronic stable angina who presents with symptoms suggestive of unstable angina. The following are the initial steps:

- Obtain ECG and cardiac enzymes
- Give aspirin
- Begin IV heparin if no contraindications (i.e., active bleeding, recent life-threatening bleed)
- Admission to hospital for workup as described above

Ischemic Heart Disease

Stable Angina Pectoris

A. General Characteristics

1. Stable angina pectoris is due to fixed atherosclerotic lesions that narrow the major coronary arteries. Coronary ischemia is due to an imbalance between blood supply and oxygen demand, leading to inadequate perfusion. Stable angina occurs when oxygen demand

exceeds available blood supply. Also called chronic coronary syndrome or stable ischemic heart disease

2. Major risk factors
   a. Diabetes mellitus (DM)—worst risk factor
   b. Hyperlipidemia—elevated low-density lipoprotein (LDL)
   c. Hypertension (HTN)—most common risk factor
   d. Cigarette smoking
   e. Age (men >45 years; women >55 years)
   f. Family history of premature CAD or MI in first-degree relative: Men <55 years; women <65 years
   g. Low levels of high-density lipoprotein (HDL)
3. Less common risk factors include end-stage renal disease (ESRD) on hemodialysis, human immunodeficiency virus (HIV) infection, history of mediastinal radiation. Minor risk factors include obesity, sedentary lifestyle (lack of physical activity), stress, excess alcohol use
4. Prognostic indicators of CAD
   a. Left ventricular function (ejection fraction [EF])
      - Normal >50%
      - If <50%, associated with increased mortality
   b. Vessel(s) involved (severity/extent of ischemia)
      - Left main coronary artery—poor prognosis because it supplies approximately two-thirds of the heart
      - Two- or three-vessel CAD—worse prognosis

Quick HIT

CAD can have the following clinical presentations:

- Asymptomatic
- Stable angina pectoris
- Unstable angina
- MI—either NSTEMI or STEMI
- Sudden cardiac death

Quick HIT

Typical Anginal Chest Pain

- Substernal
- Worse with exertion
- Better with rest or nitroglycerin

B. Clinical Features

1. Chest pain or substernal pressure sensation
   a. Lasts less than 10 to 15 minutes (usually 1 to 5 minutes)
   b. Frightening chest discomfort, usually described as heaviness, pressure, squeezing, tightness; rarely described as sharp or stabbing pain
   c. Pain is often gradual in onset
2. Brought on by factors that increase myocardial oxygen demand, such as exertion, stress, or drugs (i.e., cocaine or amphetamines)
3. Relieved with rest or nitroglycerin
4. Factors that are less consistent with ischemic pain (but do not rule out ischemia): Pain that changes with breathing or body position, or chest wall tenderness

Quick HIT

Stress testing is used in the following situations:

- To confirm diagnosis of angina
- To evaluate response to therapy in patients with documented CAD
- To identify patients with CAD who may have a high risk of acute coronary events

C. Diagnosis

1. Note that physical examination in most patients with CAD is normal. Resting ECG
   a. Usually normal in patients with stable angina
   b. Q waves are consistent with a prior MI
2. Stress test—useful for patients with an intermediate pretest probability of CAD based upon age, gender, and symptoms.

a. General principles: Exercise stress testing is preferred if the patient can exercise, whereas pharmacologic stress testing is preferred when they cannot

b. Stress ECG
   - Highest sensitivity if patients have normal resting ECG, such that changes can be noted. Patients with baseline ECG abnormalities such as left bundle branch block (LBBB), pre-existing ST-segment changes, or left ventricular hypertrophy (LVH), should NOT undergo stress ECG testing.
   - Test involves recording ECG before, during, and after exercise on a treadmill.
   - 75% sensitive if patients are able to exercise sufficiently to increase heart rate to 85% of maximum predicted value for age. A person's maximum heart rate is calculated by subtracting age from 220 (220 − age).
   - Exercise-induced ischemia results in subendocardial ischemia, producing ST-segment depression. So the detection of ischemia on a stress ECG test is based on the presence of ST-segment depression.
   - Other positive findings include onset of heart failure or ventricular arrhythmia during exercise or hypotension.
   - Patients with a positive stress test result should undergo coronary angiography.

c. Stress echocardiography
   - Performed before and immediately after exercise. Exercise-induced ischemia is evidenced by wall motion abnormalities (e.g., akinesis or hypokinesis) not present at rest. This study is less reliable in patients with existing wall motion abnormalities or lowered EF.
   - Useful to assess LV size and function, can diagnose valvular disease, and can be used to identify CAD in the presence of pre-existing ECG abnormalities (see Clinical Pearl 1-1).

d. Information gained from a stress test can be enhanced by stress myocardial perfusion imaging after IV administration of a radioisotope such as thallium 201 during exercise.
   - Viable myocardial cells extract the radioisotope from the blood. No radioisotope uptake means no blood flow to an area of the

myocardium.

- *It is important to determine whether the ischemia is reversible,* that is, whether areas of hypoperfusion are perfused over time as blood flow eventually equalizes. Areas of *reversible* ischemia may be rescued with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Irreversible ischemia, however, indicates infarcted tissue that cannot be salvaged.
- Perfusion imaging increases the sensitivity and specificity of exercise stress tests, but is also more expensive and subjects the patient to radiation.

Quick HIT

Exercise stress ECG is an ideal initial test if able to exercise and have a normal resting ECG.

Quick HIT

A stress test is generally considered positive if the patient develops any of the following during exercise: ST-segment depression, chest pain, hypotension, or significant arrhythmias.

3. If the patient cannot exercise, perform a *pharmacologic stress test.*
   a. IV adenosine, dipyridamole, or dobutamine can be used. The cardiac stress induced by these agents takes the place of exercise. This can be combined with an ECG, an echocardiogram, or nuclear perfusion imaging.
   b. IV adenosine and dipyridamole cause generalized coronary vasodilation. Since diseased coronary arteries are already maximally dilated at rest to increase blood flow, they receive relatively less blood flow when the entire coronary system is pharmacologically vasodilated. These agents are used for perfusion imaging.
   c. Dobutamine increases myocardial oxygen demand by increasing heart rate, blood pressure, and cardiac contractility. This is typically used in stress echo studies.

CLINICAL PEARL 1-1

Types of Stress Tests

Test	Method of Detecting Ischemia
Exercise ECG	ST-segment depression
Exercise or dobutamine echocardiogram	Wall motion abnormalities
Exercise or dipyridamole perfusion study (thallium/technetium)	Decreased uptake of the nuclear isotope during exercise

CLINICAL PEARL 1-2

Cardiac Catheterization

1. Most accurate method of determining a specific cardiac diagnosis.
2. Provides information on hemodynamics, intracardiac pressure measurements, cardiac output, oxygen saturation, etc.
3. Coronary angiography (see below) is almost always performed as well for visualization of coronary arteries.
4. There are many indications for cardiac catheterization (generally performed when revascularization or other surgical intervention is being considered):
   - After a positive stress test.
   - Acute MI with intent of performing angiogram and PCI.
   - In a patient with angina in any of the following situations: When noninvasive tests are nondiagnostic, angina that occurs despite medical therapy, angina that occurs soon after MI, and any angina that is a diagnostic dilemma.
   - If a patient is severely symptomatic and urgent diagnosis and management are necessary.
   - For evaluation of valvular disease, and to determine the need for surgical intervention.

Coronary Angiography

1. Most accurate method of identifying the presence and severity of CAD; the standard test for delineating coronary anatomy.
2. Main purpose is to identify patients with severe coronary disease to determine whether revascularization is needed. Revascularization with PCI involving a balloon and/or a stent can be performed at the same time as the diagnostic procedure.
3. Coronary stenosis >70% may be significant (i.e., it can produce angina).

4. Cardiac catheterization with coronary angiography (see Clinical Pearl 1-2; Figure 1-1).
   a. Coronary angiography—definitive test for CAD. Often performed with concurrent PCI or for patients being considered for revascularization with CABG.
   b. This is the test of choice for patients with very high pretest probability of CAD.
   c. Contrast is injected into coronary vessels to visualize any stenotic lesions. This defines the location and extent of coronary disease.
   d. If CAD is severe (e.g., left main or three-vessel disease, or two-vessel disease with concurrent DM), refer patient for surgical revascularization (CABG).

5. Other imaging studies to diagnose CAD include CT scan with coronary artery calcium score, or a CT angiogram. These are typically used in patients at intermediate risk who cannot exercise.

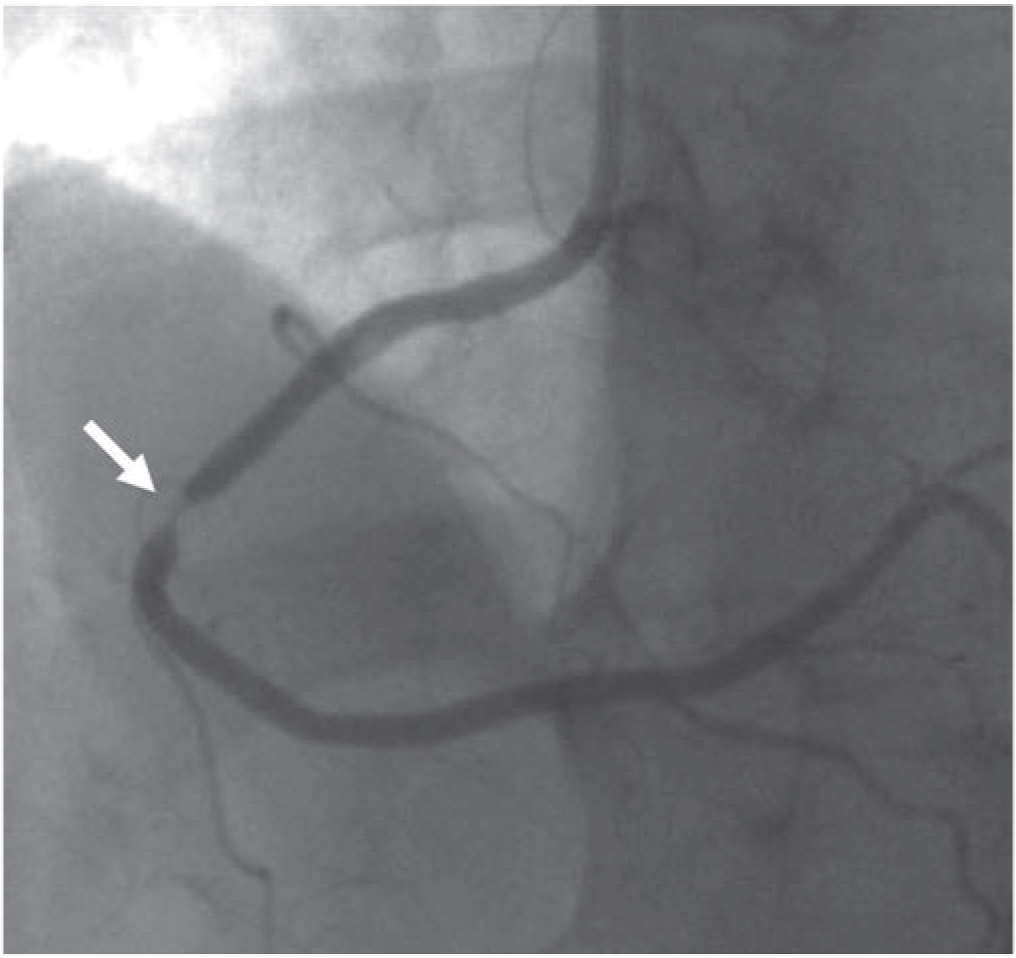


FIGURE 1-1 Coronary angiogram. Injection of the right coronary artery shows a stenosis in the midportion of the vessel, indicated by the *arrow*.
(Courtesy of Pinak B. Shah, MD, Brigham and Women's Hospital, Boston, MA.)

D. Treatment

1. Risk factor modification
   a. Smoking cessation cuts CAD risk in half by 1 year after quitting.
   b. HTN—vigorous BP control reduces the risk of CAD, especially in diabetic patients.

c. Hyperlipidemia—reduction in serum cholesterol with lifestyle modifications and HMG-CoA reductase inhibitors (statins) reduce CAD risk. Again, goal LDL is <70 mg/dL in patients with known CAD.
d. DM—type II diabetes is considered to be a cardiovascular heart disease equivalent, and strict glycemic control should be strongly emphasized.
e. Obesity—weight loss modifies other risk factors (diabetes, HTN, and hyperlipidemia) and provides other health benefits.
f. Exercise is critical; it minimizes emotional stress, promotes weight loss, and helps reduce other risk factors.
g. Diet: Reduce intake of saturated fat (<7% total calories) and cholesterol (<200 mg/day).

Quick HIT

Standard of care for stable angina includes:
- Drugs that improve mortality: Aspirin, high-intensity statins (or in some cases a PCSK9 inhibitor to lower LDL even further)
- Drugs that relieve angina: β-blockers, nitrates, calcium channel blockers, and ranolazine

Quick HIT

Side effects of β-blockers:
- Erectile dysfunction in males
- Inability to increase HR in response to exercise

Side effects of nitrates:
- Headache
- Orthostatic hypotension
- Tolerance
- Syncope

2. Medical therapy
   a. Aspirin
      - Indicated in all patients with CAD
      - Decreases morbidity—reduces risk of MI

b. Lipid-lowering therapy
   - HMG-CoA reductase inhibitors (statins) lower LDL and reduce risk of CV death
   - PCSK9 inhibitors lower LDL even further than statins and have been found to reduce CV events in patients on statin therapy with LDL levels above 70

c. β-Blockers—block sympathetic stimulation of the heart
   - Reduce HR, BP, and contractility, thereby decreasing cardiac work (i.e., β-blockers lower myocardial oxygen consumption)
   - Have been shown to reduce the frequency of coronary events

d. Nitrates—cause coronary vasodilation and systemic venodilation
   - Relieve angina; reduce preload myocardial oxygen demand
   - May prevent angina when taken before exertion
   - Effect on prognosis is unknown; main benefit is symptomatic relief
   - Can be administered orally, sublingually, transdermally, intravenously, or in paste form. For chronic angina, oral or transdermal patches are used. For acute coronary syndromes (see below), either sublingual, paste, or IV forms are used

e. Calcium channel blockers (CCBs)
   - Cause coronary vasodilation and afterload reduction, reduce contractility
   - Add to antianginal therapy when β-blockers and nitrates are not fully effective

3. Revascularization
   a. Controversial for patients with stable CAD, as studies suggest no improvement in mortality and MI (when compared to medical therapy alone). Per guidelines, revascularization is indicated for stable angina refractory to medical therapy for symptom control.
   b. Two methods—PCI and CABG—see Clinical Pearl 1-3.

4. Management decisions (general guidelines)—risk factor modification and aspirin are indicated in all patients. Manage patients according to overall risk
   a. Mild disease (normal EF, mild angina, single-vessel disease)
      - Nitrates (for symptoms and as prophylaxis) and a β-blocker are appropriate

- Consider CCBs if symptoms continue despite nitrates and β-blockers

b. Moderate disease (normal EF, moderate angina, two-vessel disease)
  - If the above regimen does not control symptoms, consider coronary angiography to assess suitability for revascularization (either PCI or CABG)

c. Severe disease (reduced EF, severe angina, and three-vessel/left main or left anterior descending [LAD] disease)
  - Coronary angiography and consider for CABG
  - Avoid CCBs with reduced EF

Quick HIT

The COURAGE trial showed essentially no difference in all-cause mortality and nonfatal MIs between patients with stable angina treated with maximal medical therapy alone versus medical therapy with PCI and bare metal stenting. Of note, most PCI is now done with drug-eluting stents which are superior to bare metal stents with regard to risk of stent thrombosis and recurrent MI.

CLINICAL PEARL 1-3

Percutaneous Coronary Intervention

- Consists of both coronary angioplasty with a balloon and stenting.
- Should be considered in patients with one-, two-, or three-vessel disease. Even with three-vessel disease, mortality and freedom from MI have been shown to be equivalent between PTCA with stenting and CABG. The only drawback is the higher frequency of revascularization procedures in patients who received a stent.
- Best if used for proximal lesions.
- Restenosis is a significant problem (up to 40% within first 6 months); however, if there is no evidence of restenosis at 6 months, it usually does not occur. New techniques and technologic improvements such as drug-eluting stents are attempting to reduce this problem.

Coronary Artery Bypass Grafting

- While CABG remains the standard of care at some institutions for patients with high-risk disease, the PRECOMBAT and SYNTAX trails have shown that PTCA with stenting may be as good as CABG even in patients with left main CAD. CABG is still used as the primary method of revascularization in a small number of patients with STEMI. In addition, it may be indicated in patients with cardiogenic shock post-MI, after complications with PCI, in the setting of ventricular arrhythmias, and with mechanical complications after acute MI.
- Main indications for CABG: Three-vessel disease with >70% stenosis in each vessel. Left main coronary disease with >50% stenosis, left ventricular dysfunction.

Acute Coronary Syndromes (ACS)

A. Background and Terminology

1. Terminology
   a. ACS includes UA, NSTEMI, and STEMI
   b. The distinction between UA and NSTEMI is based entirely on cardiac enzymes. Both UA and NSTEMI lack ST-segment elevations, differentiating them from STEMI
   c. UA is differentiated from stable angina if it has any of the following characteristics:
      - New onset angina
      - Angina at rest (without exertion)
      - Early post-MI or post-PCI

d. With the more widespread use of high-sensitivity troponin testing, UA is a rare diagnosis since virtually all cases of ACS will have an elevation in this biomarker. Thus, UA is more of a historical term, and the priority in clinical care is differentiating and managing NSTEMI versus STEMI
e. MI occurs in NSTEMI and STEMI, and is defined as an elevation in a cardiac biomarker with evidence of acute myocardial ischemia

2. Pathophysiology
   a. With UA, *oxygen demand is unchanged*. Supply is decreased secondary to *reduced resting coronary flow*. This is in contrast to stable angina, which is due to increased demand.
   b. UA is significant because it indicates stenosis that has enlarged via thrombosis, hemorrhage, or plaque rupture. It may lead to total occlusion of a coronary vessel. UA has a higher risk of MI and death than stable angina, and patients with this diagnosis should be hospitalized.
   c. MI is due to necrosis of myocardium as a result of an interruption of blood supply.
      - Most cases are due to acute coronary thrombosis: Atheromatous plaque ruptures into the vessel lumen, and thrombus forms on top of this lesion, which causes occlusion of the vessel.
      - MI is associated with a 30% mortality rate; half of the deaths are prehospital.
      - Most patients with MI have history of angina, risk factors for CAD, or history of arrhythmias.
   d. A 2018 Joint Task Force subclassified MI into five categories:
      - Type 1 MI: Plaque rupture with thrombus
      - Type 2 MI: A supply–demand mismatch with oxygen delivery
      - Type 3 MI: Typical MI suspected, but death occurs without testing the blood for cardiac biomarker elevation
      - Type 4 MI: MI associated with PCI
      - Type 5 MI: MI associated with CABG

Quick HIT

Acute Coronary Syndrome

- The clinical manifestations of atherosclerotic plaque rupture and coronary occlusion
- Term generally refers to UA, NSTEMI, or STEMI

Quick HIT

The combination of substernal chest pain persisting for longer than 30 minutes and diaphoresis strongly suggests acute MI.

B. Clinical Features

1. Chest pain
   a. Intense substernal pressure sensation; often described as "crushing" and "an elephant standing on my chest"
   b. Radiation to neck, jaw, arms, or back, commonly to the left side
   c. Similar to angina pectoris in character and distribution but much more severe and lasts longer. Unlike in angina, pain may not respond to nitroglycerin
   d. Some patients may have epigastric discomfort
2. *Can be asymptomatic in up to one-third of patients;* painless infarcts or atypical presentations more likely in postoperative patients, the elderly, diabetic patients, and women
3. Other symptoms
   a. Dyspnea
   b. Diaphoresis
   c. Weakness, fatigue
   d. Nausea and vomiting
   e. Sense of impending doom
   f. Syncope
4. Sudden cardiac death—usually due to ventricular fibrillation (VFib)

Quick HIT

The majority of ACS cases are diagnosed as NSTEMI or STEMI. UA is now rare with high-sensitivity troponin testing.

A 59-year-old woman presents to your office with chest discomfort, jaw pain, and nausea. The symptoms occurred suddenly 2 hours ago and are getting worse. She has a history of poorly controlled hypertension, and she has a 30 pack-year smoking history. You send her to the emergency department and order some initial tests, which are shown below.

Sodium	137 mEq/L
Potassium	4.9 mEq/L
Chloride	105 mEq/L
Bicarbonate	22 mEq/L
Blood urea nitrogen	21 mg/dL
Creatinine	1.3 mg/dL
Glucose	110 mg/dL
High sensitivity troponin	Positive

An ECG shows multiple T-wave inversions and ST depressions in contiguous leads.

Which of the following is the most likely diagnosis?

A. Stable angina
B. Unstable angina
C. Non-ST elevation myocardial infarction
D. ST elevation myocardial infarction

- **The answer is C: Non-ST elevation myocardial infarction.** It is important to know how to differentiate the types of ACS, since this guides the course of action as well as the prognosis. ACS is made up of unstable angina, non-ST elevation myocardial infarction (NSTEMI), and STEMI. **(A, B)** Stable angina is not an ACS, and typically occurs with a consistent level of exertion that is relieved with rest and/or nitroglycerin; however, it can progress to unstable angina which typically lasts less than 30 minutes and manifests as

angina without exertion, angina with a crescendo pattern, or angina that is severe and of new onset. **(C, D)** NSTEMI is differentiated from unstable angina by positive troponins, and STEMI is differentiated from NSTEMI by ST elevations seen on ECG. In unstable angina and NSTEMI, there may or may not be ST depression and T-wave inversions (signs of myocardial ischemia), but there will not be ST elevations.

***Quick* HIT**

Stress testing only detects flow-limiting high-grade lesions. Thus, can still have MI despite negative stress test because mechanism of MI is acute plaque rupture onto a moderate lesion.

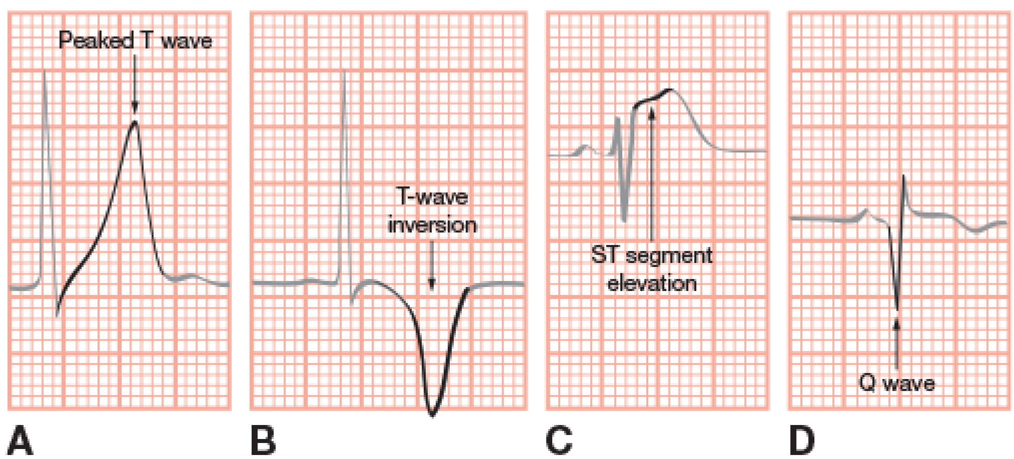


FIGURE 1-2 **ST-segment patterns consistent with STEMI. (A) During the early stage of infarction, T waves are tall and peaked. (B) Within a few hours, the T waves invert. (C) Then, the ST segment elevates, lasting several hours to several days. (D) Q waves indicative of infarction develop within several hours of the infarction but in some patients they do not develop until 24 to 48 hours later.**
(Reprinted with permission from Diepenbrock NH. *Quick Reference to Critical Care*. 6th ed. Wolters Kluwer; 2020. Figure 2-55.)

Quick HIT

ST-segment elevation indicates an infarction 75% of the time. ST-segment depression indicates an infarction only 25% of the time.

C. Diagnosis

1. Initial approach: For all patients should, at minimum, include a brief history and physical, lab testing (including cardiac biomarkers, especially high-sensitivity troponin if available), and an ECG.
   a. For patients with an initial normal troponin, it should be repeated in 3 to 6 hours.
   b. The ECG can be repeated every 15 to 30 minutes to evaluate for dynamic changes.
   c. A bedside ultrasound can also be useful to evaluate cardiac function and regional wall motion abnormalities.
2. ECG (Figure 1-2; see also Table 1-1 and Clinical Pearl 1-4)
   a. Markers for ischemia/infarction include:
      - **Peaked T waves:** Occur very early and may be missed
      - **ST-segment elevation** indicates transmural injury and can be diagnostic of an acute infarct
      - **Q waves:** Evidence for necrosis (specific)—Q waves are usually seen late; typically not seen acutely
      - **T-wave** inversion is sensitive but not specific
      - **ST-segment depression:** Subendocardial injury
   b. Categories of infarcts
      - **ST-segment elevation infarct:** Transmural (involves entire thickness of wall); tends to be larger. For an MI to be categorized as a STEMI, there must be ST-segment elevation in two contiguous leads (e.g., II and III). This elevation must be at least 0.1 mV (1 mm, or 1 small box) in all the leads except V2–V3: at least 0.2 mV or 2 mm in men ≥40 years old, at least 0.25 mV or 2.5 mm in men <40 years old, or ≥0.15 mV or 1.5 mm in women.
      - **Non–ST-segment elevation infarct:** Subendocardial (involves inner one-third to one-half of the wall); tends to be smaller, and presentation is similar to UA—cardiac enzymes differentiate the two.

Quick HIT

STEMI diagnosis: ST elevation in two contiguous leads of at least 1 mm (1 small box on ECG). If the ST elevation is in V2 or V3, the threshold is higher (≥2 mm in men ≥40 years old, ≥2.5 mm in men <40 years old, and ≥1.5 in women).

TABLE 1-1 ECG Findings Based on Location of Infarct

Location of Infarct	ECG Changes
Anterior	ST-segment elevation in V1–V4 (acute/active)
	Q waves in leads V1–V4 (late change)
Posterior	Large R wave in V1 and V2 ST-segment depression in V1 and V2 Upright and prominent T waves in V1 and V2
Lateral	Q waves in leads I and aVL (late change)
Inferior	Q waves in leads II, III, aVF (late change)

Note: Augmented ECG leads from aVL indicate the left arm, and from aVF indicate the left foot.

CLINICAL PEARL 1-4

Cardiac Monitoring for a Patient With an Acute MI

- BP and HR: HTN increases afterload and thus oxygen demand, whereas hypotension reduces coronary and tissue perfusion. Both nitrates and morphine can cause hypotension.
- Telemetry (cardiac monitoring): Watch for dysrhythmias. Note that PVCs can lower stroke volume and coronary artery filling time. A high frequency of PVCs may predict VFib or VT.
- Auscultate the heart (third and fourth heart sounds, friction rub, and so on) and lungs (crackles may indicate LV failure, pulmonary edema).
- Hemodynamic monitoring (CVP, PCWP, SVR, cardiac index [CI]) with a pulmonary artery catheter can be considered in unstable patients. Monitoring is helpful in assessing the need for IV fluids and/or vasopressors.

3. Cardiac enzymes—elevated in the setting of myocardial injury (Figure 1-3)
   a. Troponins (troponin I and T)—the preferred test when MI is suspected.
      - High-sensitivity troponin assays can be elevated within 2 to 3 hours of presentation. Routine troponin I and T assays can be elevated within 3 to 5 hours and return to normal in 5 to 14 days (peaks in 24 to 48 hours).
      - Greater sensitivity and specificity than CK-MB for myocardial injury.
      - Obtain serum troponin level at presentation, and 3 to 6 hours later.
      - Troponins are highly sensitive and specific for cardiac injury, however not all troponin elevations indicate MI (myocarditis, heart failure, etc.).
   b. CK-MB—less commonly used
      - Increases within 4 to 8 hours and returns to normal in 48 to 72 hours; reaches a peak in 24 hours.
      - Troponin assays have mostly replaced the use of CK-MB in clinical practice.

Quick HIT

Cardiac enzymes are drawn serially—once on admission and again in 3 to 6 hours. The higher the peak and the longer enzyme levels remain elevated, the more severe the myocardial injury and the worse the prognosis.

Quick HIT

The CAPRICORN trial showed that the β-blocker carvedilol reduces the risk of death in patients with post-MI LV dysfunction.

D. Treatment (see Figure 1-4)

1. Initial management of all patients:
   a. Hospital admission on a floor with continuous cardiac monitoring. Establish IV access and give supplemental oxygen if patients are

hypoxic. Monitor and aggressively replete electrolytes.

b. Manage other complications as indicated (arrhythmias per ACLS protocols, afterload-reducing agents for heart failure, etc.).
c. Aspirin 325 mg and atorvastatin 80 mg.
    - The PROVE IT-TIMI 22 trial showed the superiority of starting atorvastatin 80 mg over other statins before discharging a STEMI patient.
d. Nitrates for chest pain, which cause coronary dilation and increase oxygen supply to the myocardium. Nitroglycerin first as sublingual tablet or spray, if persistent pain can start an IV drip. Avoid if hypotension, RV infarct/failure, or recent use of phosphodiesterase inhibitor (e.g., sildenafil).
e. Morphine IV can be used with caution if ongoing pain and anxiety not relieved by nitrates. Also causes venodilation and reduces preload.
f. Give a β-blocker such as metoprolol if no hypotension or heart failure.
    - Block stimulation of HR and contractility to reduce oxygen demand and decrease the incidence of arrhythmias.
    - Reduce remodeling of the myocardium post-MI.

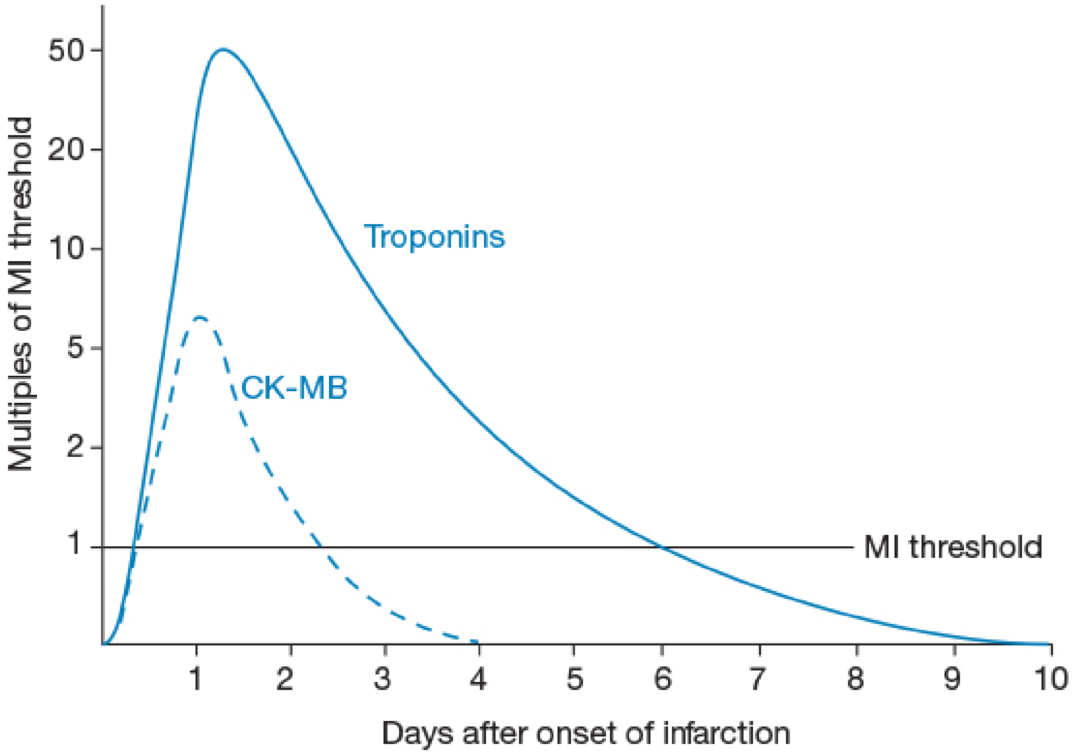


FIGURE 1-3 **Evolution of serum biomarkers in acute MI. Curve M indicates the detection of myoglobin in the serum before other biomarkers. Serum CK (or CK-MB isoenzyme) begins to increase 3 to 8 hours after the onset of the acute infarct and peaks at 24 hours. Cardiac troponins are highly sensitive for myocardial injury and remain detectable in the serum for many days after the acute infarct.**

(Reprinted with permission from Lilly LS. *Pathophysiology of Heart Disease*. 3rd ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011:175. Figure 7.9.)

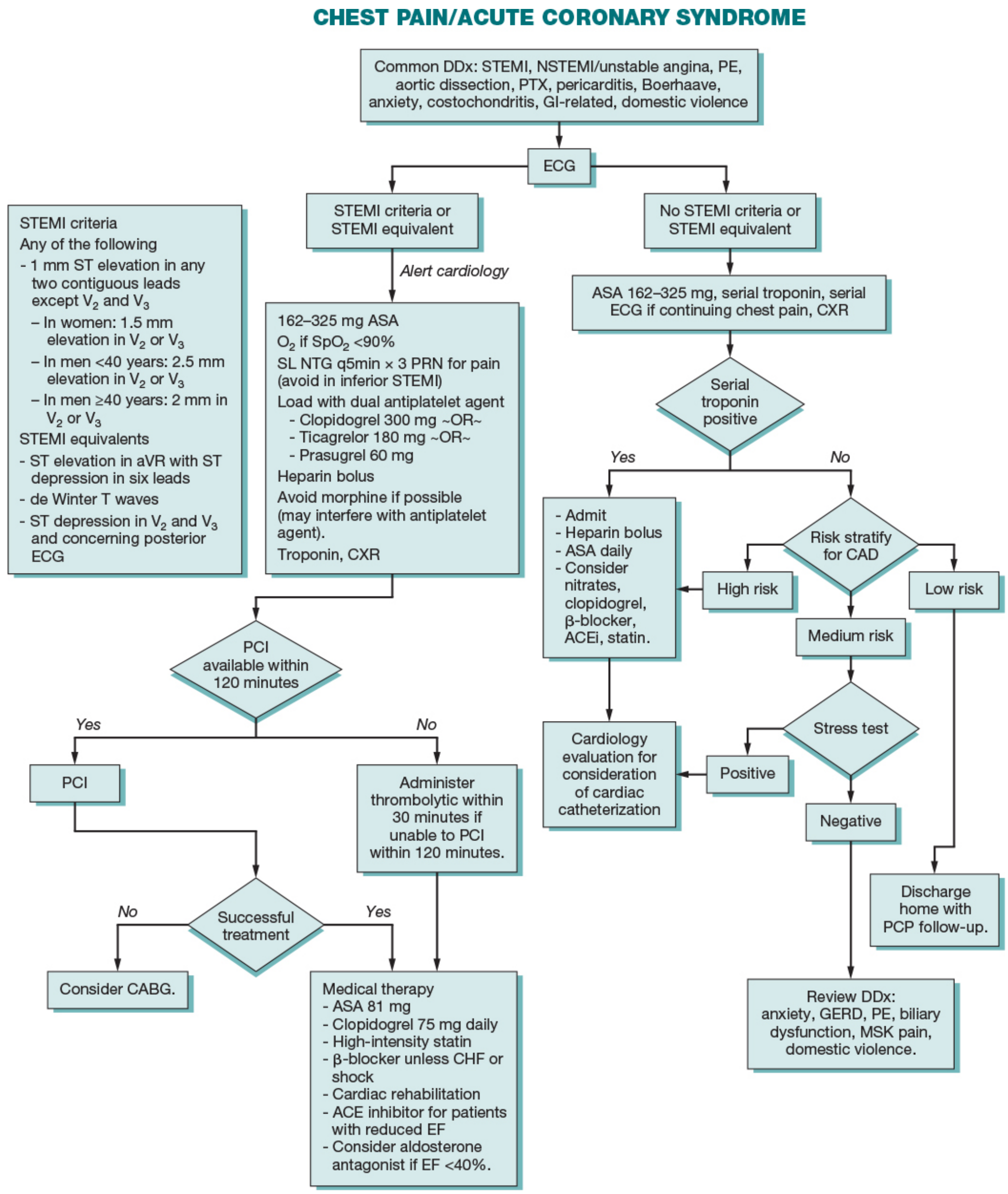


FIGURE 1-4 **Chest Pain/Acute Coronary Syndrome.**
(Reprinted with permission from Domino FJ, Baldor RA, Barry KA, et al. *The 5-Minute Clinical Consult 2023*. 31st ed. Wolters Kluwer, 2022. [Data from Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231–2264].)

2. Treatment of NSTEMI and STEMI

   a. Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor, prasugrel). Anticoagulation with heparin or

bivalirudin if undergoing cardiac catheterization, enoxaparin or fondaparinux for those not undergoing catheterization. Goal is to prevent development or progression of a clot. Duration of treatment is at least 48 hours

b. Advanced therapies
   - Fibrinolysis
   - Not beneficial in NSTEMI, should only consider in STEMI.
   - For STEMI, PCI is preferred to fibrinolysis as long as it can be performed within 120 minutes of presentation. Ideally, PCI is performed within 90 minutes of presentation (door-to-balloon time)
   - Fibrinolysis is considered if symptoms began within the past 12 hours, and if PCI is not available within 120 minutes. Fibrinolytic (e.g., alteplase, tenecteplase) should be given within 30 minutes of presentation

c. Revascularization:
   - Some NSTEMI patients benefit from early coronary angiography and revascularization: New heart failure, cardiogenic shock, persistent angina despite medical therapy, ventricular arrhythmias, or other high-risk patients (can use the TIMI or GRACE score to help risk stratify)
   - STEMI: All patients should undergo PCI if it is readily available. It improves mortality and risk of recurrent MI

3. After the acute treatment
   a. Continue aspirin (or other antiplatelet therapy), β-blockers (metoprolol), nitrates, and statin therapy
   b. Reduce risk factors
      - Smoking cessation, weight loss
      - Treat diabetes, HTN
      - Treat hyperlipidemia—patients with any form of CAD should be started on an HMG-CoA reductase inhibitor regardless of LDL level. Clinical trials of statins have shown the efficacy of such therapy for secondary prevention in CAD (see Quick Hit on CARE trial)
   c. Cardiac rehabilitation is a physician-supervised regimen of exercise and risk factor reduction after MI, and can reduce symptoms and prolong survival

Quick HIT

The following are indicated in patients with MI:

- Aspirin
- P2Y12 inhibitor
- Nitroglycerin for chest pain
- β-Blocker
- ACE inhibitor (ACEi)
- Heparin
- Oxygen if hypoxic
- Morphine if chest pain unrelieved with nitrates

Quick HIT

Right ventricular infarct will present with inferior ECG changes, hypotension, elevated jugular venous pressure, hepatomegaly, and clear lungs. Preload dependent—do NOT administer nitrates or diuretics as these can cause cardiovascular collapse.

Quick HIT

The **ESSENCE** trial showed that in UA and non–ST-segment elevation MI, risk of death, MI, or recurrent angina was lower in the enoxaparin group than in the heparin group at 14 days, 30 days, and 1 year. The need for revascularization was also lower in the enoxaparin group.

Quick HIT

Thrombolytic therapy (fibrinolysis) has NOT been proven to be beneficial in UA or NSTEMI. This is only indicated in STEMI when no access to urgent catheterization for PCI.

Quick HIT

The **CARE** trial: Patients with prior history of MI were randomized to treatment with statins or placebo. The statin group had a reduced risk of death (by 24%), a reduced risk of stroke (by 31%), and a reduction in need for CABG or coronary angioplasty (by 27%).

Quick HIT

All patients initially treated conservatively (i.e., without revascularization) for UA/NSTEMI should have a stress test before leaving the hospital to determine the need for angiography (which in turn determines the need for angioplasty or CABG).

E. Complications of Acute MI

1. Pump failure (congestive heart failure [CHF]) (Figure 1-5)
   a. Most common cause of in-hospital mortality
   b. If mild, treat medically (ACEi, diuretic)
   c. If severe, may lead to cardiogenic shock; invasive hemodynamic monitoring or support with inotropes or devices may be indicated (see Cardiogenic Shock on page 64)
2. Arrhythmias
   a. Premature ventricular contractions (PVCs)—conservative treatment (observation) indicated; no need for antiarrhythmic agents
   b. Atrial fibrillation (AFib)
   c. Ventricular tachycardia (VT)–sustained VT requires treatment: If patient is hemodynamically unstable, electrical cardioversion is indicated. If patient is hemodynamically stable, start antiarrhythmic therapy—see treatment of VT
   d. VFib—immediate unsynchronized defibrillation and CPR are indicated (see Arrhythmias on page 21)
   e. Accelerated idioventricular rhythm does not affect prognosis; no treatment needed in most cases
   f. Paroxysmal supraventricular tachycardia (PSVT)—for treatment, see Arrhythmias
   g. Sinus tachycardia

- May be caused by pain, anxiety, fever, pericarditis, medications, etc.
- Worsens ischemia (increases myocardial oxygen consumption)
- Treat underlying cause (analgesics for pain, acetaminophen for fever, etc.)

h. Sinus bradycardia
- A common occurrence in early stages of acute MI, especially right-sided/inferior MI
- May be a protective mechanism (reduces myocardial oxygen demand)
- No treatment is required other than observation. If bradycardia is severe or symptomatic (hemodynamic compromise), atropine may be helpful in increasing HR

i. Asystole
- Very high mortality
- Treatment should begin with electrical defibrillation for VFib, which is more common in cardiac arrest and may be difficult to clearly differentiate from asystole
- If asystole is clearly the cause of arrest, transcutaneous pacing is the appropriate treatment

j. AV block
- Associated with ischemia involving conduction tracts
- First- and second-degree (type I) blocks do not require therapy
- Second- (type II) and third-degree blocks: Prognosis is dire in the setting of an *anterior* MI—emergent placement of a temporary pacemaker is indicated (with later placement of a permanent pacemaker). In inferior MI, prognosis is better, and IV atropine may be used initially. If conduction is not restored, a temporary pacemaker is appropriate. Can use positive chronotropic medications to maintain HR and blood pressures (i.e., isoproterenol or dopamine) while awaiting placement of temporary pacemaker

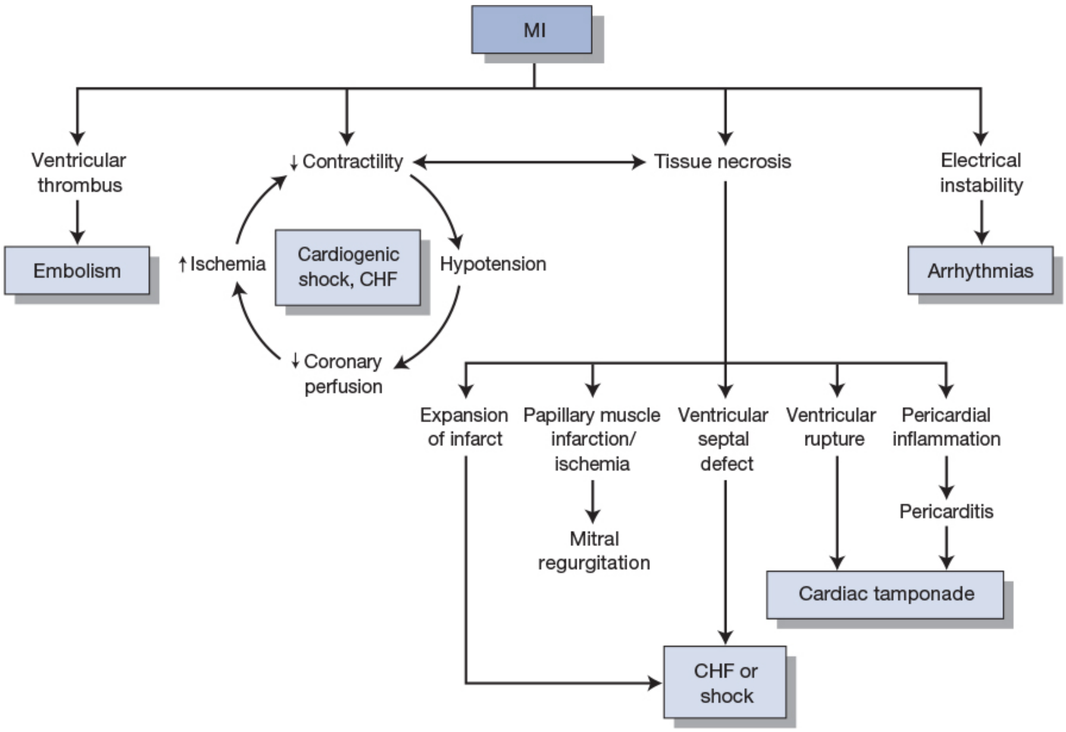


FIGURE 1-5 **Complications of MI.**

Quick HIT

Patients who suffer an acute MI have a high risk of stroke during the next 5 years. The lower the EF and the older the patient, the higher the risk of stroke.

Quick HIT

Most common cause of death in the first few days after MI is ventricular arrhythmia (either VT or VFib).

Quick HIT

After an MI, all patients should be discharged home with aspirin, β-blocker, statins, and an ACEi, and a P2Y12 inhibitor if indicated.

3. Recurrent infarction (extension of existing infarction or reinfarction of a new area)
   a. Both short- and long-term mortality are increased.
   b. Diagnosis is often difficult.
      - Cardiac enzymes are already elevated from the initial infarction. Troponin levels remain elevated for a week or more, so are not useful here. CK-MB returns to normal faster, and so a reelevation of CK-MB after 36 to 48 hours may be due to recurrent infarction.
      - If there is *repeat ST-segment elevation* on ECG within the first 24 hours after infarction, suspect recurrent infarction or LV aneurysm.
   c. Treatment: Repeat thrombolysis or urgent cardiac catheterization and PCI. Continue standard medical therapy for MI.
4. Mechanical complications
   a. Free wall rupture
      - A catastrophic, usually fatal event that occurs during the first 2 weeks after MI (90% within 2 weeks, most commonly 1 to 4 days after MI)
      - 90% mortality rate
      - Usually leads to hemopericardium and cardiac tamponade
      - Treatment: Hemodynamic stabilization, immediate pericardiocentesis, and surgical repair
   b. Rupture of interventricular septum
      - Greater potential for successful therapy than with a free wall rupture, although this is also a critical event; emergent surgery is indicated
      - Occurs within 10 days after MI
      - Likelihood of survival correlates with size of the defect
   c. Papillary muscle rupture
      - *Produces acute MR* (presents with new murmur)
      - If suspected, obtain an echocardiogram immediately
      - Emergent surgery is needed (mitral valve replacement is usually necessary), as well as afterload reduction with sodium nitroprusside or intraaortic balloon pump (IABP)
   d. Ventricular pseudoaneurysm
      - *Incomplete* free wall rupture (myocardial rupture is contained by pericardium)

- Bedside echocardiogram may show the pseudoaneurysm
- Surgical emergency because ventricular pseudoaneurysms tend to become a free wall rupture

e. Ventricular aneurysm
- Rarely rupture (in contrast to pseudoaneurysms)
- Associated with a high incidence of ventricular tachyarrhythmias
- Medical management may be protective
- Surgery to remove aneurysm may be appropriate in selected patients

5. Acute pericarditis
   a. The incidence has decreased sharply since the introduction of revascularization techniques
   b. Treatment consists of aspirin (which is already standard in treatment of MI)
   c. NSAIDs and corticosteroids are contraindicated (may hinder myocardial scar formation)
6. *Dressler syndrome* (“postmyocardial infarction syndrome”)
   a. Immunologically based syndrome consisting of fever, malaise, pericarditis, leukocytosis, and pleuritis, occurring weeks to months after an MI
   b. Aspirin is the most effective therapy. Ibuprofen is a second option

A 73-year-old woman is brought in by paramedics after “passing out” in the mall and hitting her face. She does not remember any preceding symptoms, and she did not lose control of her bowel or bladder. Witnesses at the scene say that she was down for less than a minute, then woke up and was fairly alert. She was bleeding from a laceration on her chin and paramedics were called. When she arrived at the hospital, her initial labs were normal. She is placed on a cardiac monitor. The following day, she becomes lightheaded and loses consciousness while lying in bed, and her monitor shows tachycardia with the QRS complexes being uniformly longer than 120 ms.

What is the most common cause of this rhythm disturbance?

A. Uncontrolled hypertension
B. Distention of the pulmonary veins
C. Accessory pathway
D. Ischemic heart disease

- **The answer is D: Ischemic heart disease.** The vignette describes an episode of ventricular tachycardia, which is indicated by the wide QRS complexes on her monitor. A serious arrhythmia should have been high on the differential given her episode of syncope with the red flag of head trauma, indicating a very sudden loss of consciousness without any ability to brace herself, which is typical of a cardiac etiology. The most common cause of ventricular tachycardia is ischemic heart disease. Patients that suffer a myocardial infarction have scarring of the myocardium that disrupts the normal electrical pathways and increases the risk of developing this dangerous rhythm. **(A, C)** Uncontrolled hypertension and accessory pathways are not the most common causes of ventricular tachycardia. **(B)** Distention of the pulmonary veins is thought to be a mechanism of atrial fibrillation.

Variant (Prinzmetal) Angina

- Involves transient coronary vasospasm that usually is accompanied by a fixed atherosclerotic lesion but can also occur in normal coronary arteries.
- Episodes of angina occur at rest and are associated with ventricular arrhythmias, some of which may be life threatening. The angina classically occurs at night.
- Hallmark is transient ST-segment elevation (not depression) on ECG during chest pain, which represents transmural ischemia.
- Coronary angiography is a definitive test—displays coronary vasospasm when the patient is given IV ergonovine or acetylcholine (to provoke vasoconstriction).
- Vasodilators—CCBs and nitrates have been proven to be helpful. Risk factor modification including smoking cessation and lipid lowering is also indicated where appropriate.

Quick HIT

Often, both systolic and diastolic dysfunctions are present simultaneously.

Congestive Heart Failure

A. General Characteristics

1. CHF is a clinical syndrome resulting from the heart's inability to meet the body's circulatory demands under normal physiologic conditions. It is the final common pathway for a wide variety of cardiac diseases (see also Clinical Pearl 1-5)
2. Pathophysiology (Figure 1-6)
   a. Frank–Starling relationship
      - In a normal heart, increasing preload results in greater contractility
      - When preload is low (at rest), there is little difference in performance between a normal and a failing heart. However, with exertion a failing heart produces relatively less contractility and symptoms occur (Figure 1-7)

3. Heart Failure with reduced Ejection Fraction (HFrEF) or systolic dysfunction
   a. Owing to impaired contractility (reduced EF <40%)
   b. Causes include:
      - Ischemic heart disease or after a recent MI—infarcted cardiac muscle does not pump blood (decreased EF)
      - Idiopathic
      - HTN
      - Myocarditis (postviral, giant cell, autoimmune)
      - Drugs: Alcohol, cocaine, methamphetamines, chemotherapy (anthracyclines and trastuzumab)
      - Infiltrative disease (amyloidosis, sarcoidosis, hemochromatosis, Wilson disease)
      - Radiation therapy
      - Thyroid disease
      - Peripartum cardiomyopathy
      - Infectious disease (Chagas disease, HIV, endocarditis causing valvular disease)
      - Valvular heart disease (usually MR, aortic stenosis [AS] or regurgitation)
      - High-output heart failure (severe anemia, due to AV fistulas, pregnancy, severe thiamine deficiency)
      - Congenital/hereditary

CLINICAL PEARL 1-5

High-Output Heart Failure

1. In high-output heart failure, an increase in cardiac output is needed for the requirements of peripheral tissues for oxygen.
2. Causes include:
   - Chronic anemia
   - Pregnancy
   - Hyperthyroidism
   - AV fistulas
   - Wet beriberi (caused by thiamine [vitamin B_1] deficiency)
   - Paget disease of bone
   - MR
   - Aortic insufficiency
3. The conditions listed above rarely cause heart failure by themselves. However, if these conditions develop in the presence of underlying heart disease, heart failure can result quickly.

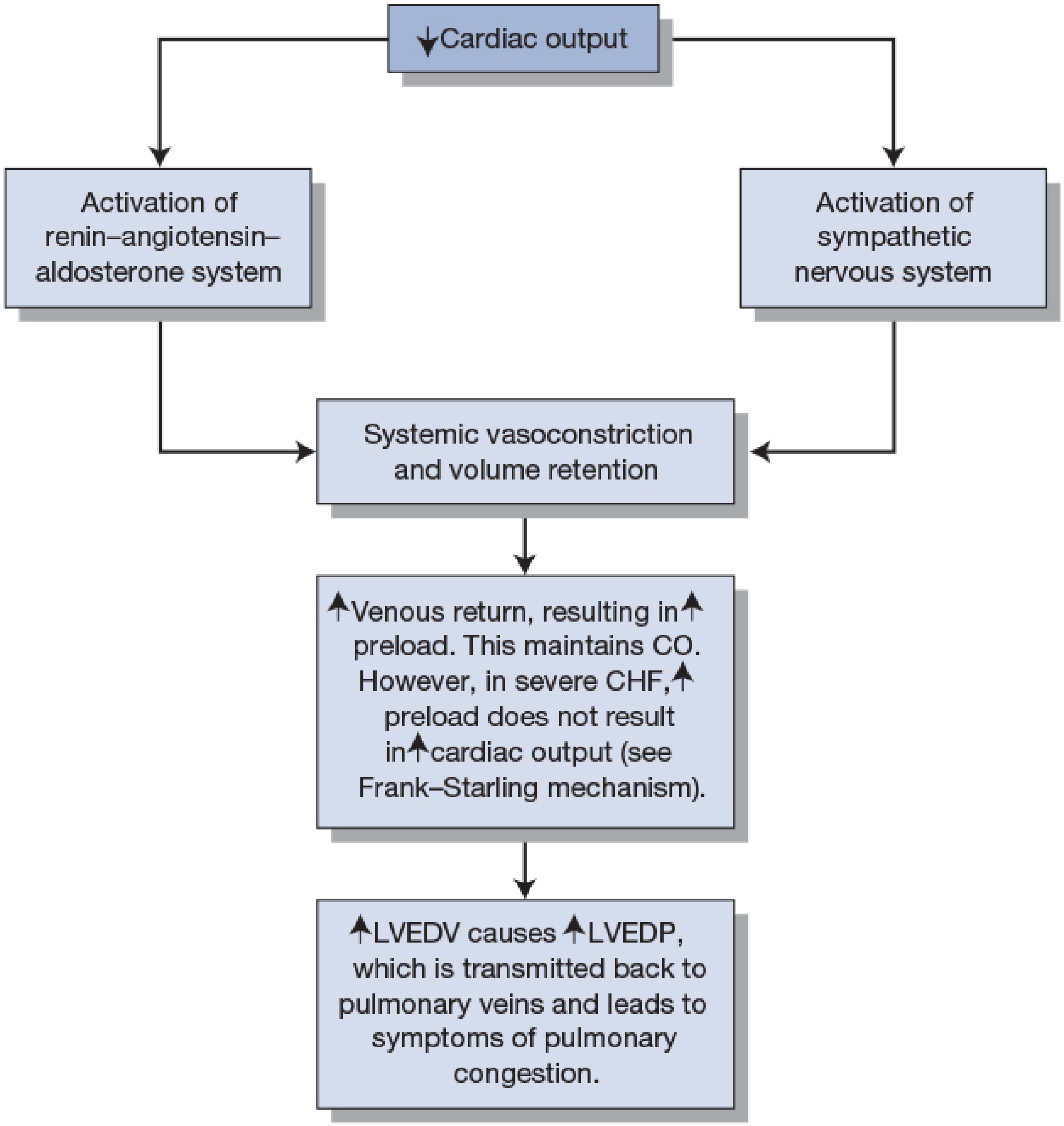


FIGURE 1-6 **Pathophysiology of CHF.**

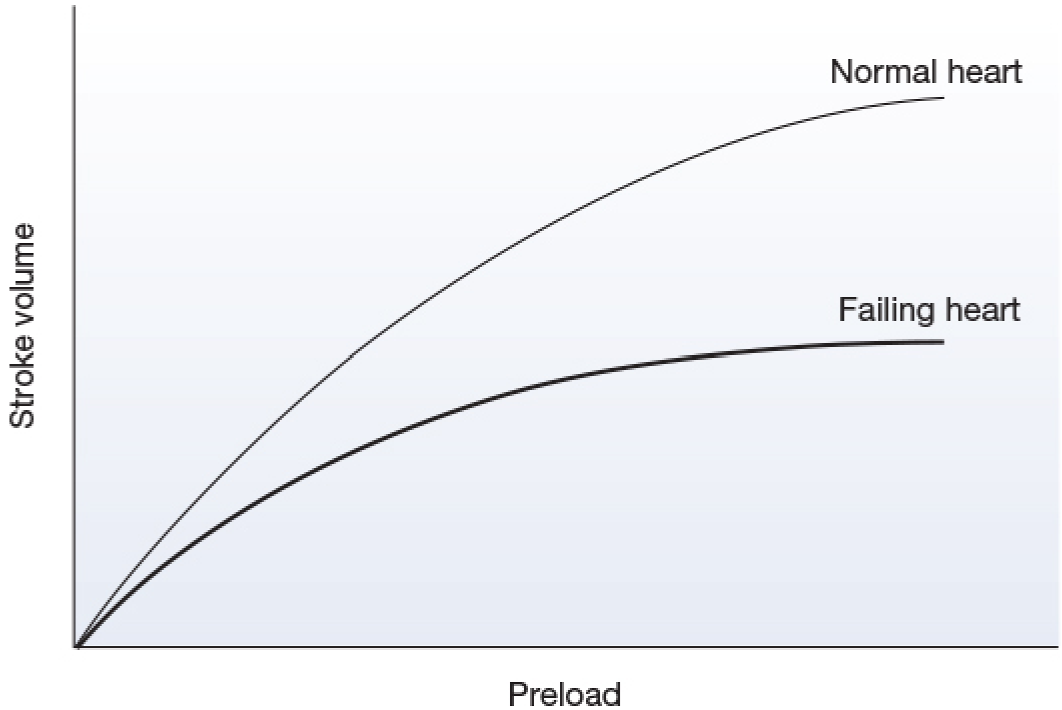


FIGURE 1-7 **Frank–Starling relationship.**

4. Heart Failure with preserved Ejection Fraction (HFpEF) or diastolic dysfunction
   a. Owing to impaired ventricular filling during diastole (either impaired relaxation or increased stiffness of ventricle or both)
   b. Echocardiogram shows impaired relaxation of left ventricle but EF >50%
   c. Causes include:
      - HTN leading to myocardial hypertrophy—most common cause of diastolic dysfunction
      - Valvular diseases such as AS, mitral stenosis, and aortic regurgitation
      - Restrictive cardiomyopathy (e.g., amyloidosis, sarcoidosis, hemochromatosis in their early phases)
5. Heart Failure with mid-range Ejection Fraction (HFmrEF)
   a. Newer terminology for patients with an EF between 40% and 50%
   b. Pathophysiology and outcomes typically on the spectrum between HFrEF and HFpEF

B. Clinical Features

1. Symptoms of left-sided heart failure (see also Clinical Pearl 1-6)
   a. Dyspnea—difficulty breathing secondary to pulmonary congestion/edema
   b. *Orthopnea*—difficulty breathing in the recumbent position; relieved by elevation of the head with pillows
   c. *Paroxysmal nocturnal dyspnea* (PND)—awakening after 1 to 2 hours of sleep due to acute shortness of breath (SOB)
   d. Nocturnal cough (nonproductive)—worse in recumbent position (same pathophysiology as orthopnea)
   e. Confusion and memory impairment occur in advanced CHF as a result of inadequate brain perfusion
   f. Diaphoresis and cool extremities at rest—occur in desperately ill patients (NYHA class IV)

CLINICAL PEARL 1-6

New York Heart Association (NYHA) Classification

- NYHA class I: Symptoms only occur with vigorous activities, such as playing a sport. Patients are nearly asymptomatic.
- NYHA class II: Symptoms occur with prolonged or moderate exertion, such as climbing a flight of stairs or carrying heavy packages. Slight limitation of activities.
- NYHA class III: Symptoms occur with usual activities of daily living, such as walking across the room or getting dressed. Markedly limiting.
- NYHA class IV: Symptoms occur at rest. Incapacitating.

2. Signs of left-sided heart failure
   a. Displaced PMI (usually to the left) due to cardiomegaly
   b. Pathologic S_3 (ventricular gallop)
      - Rapid filling phase "into" a noncompliant left ventricular chamber
      - May be normal finding in children; in adults, usually associated with CHF
      - May be difficult to hear, but is among the most specific signs of CHF
      - Heard best at apex with bell of stethoscope

- The sequence in the cardiac cycle for S_3: S_3 follows S_2 (ken-tuck-*Y*)

c. S_4 gallop
   - Sound of atrial systole as blood is ejected into a noncompliant, or stiff, left ventricular chamber
   - Heard best at left sternal border with bell of stethoscope
   - The sequence in the cardiac cycle for S_4: S_4 precedes S_1 (*TEN*-nes-see)

d. Crackles/rales at lung bases
   - Caused by fluid spilling into alveoli; indicates pulmonary edema
   - Rales heard over lung bases suggest at least moderate severity of left ventricular heart failure

e. Dullness to percussion and decreased tactile fremitus of lower lung fields caused by pleural effusion

f. Increased intensity of pulmonic component of second heart sound suggests pulmonary HTN (heard over left upper sternal border)

3. Symptoms/signs of right-sided heart failure
   a. Peripheral pitting edema—pedal edema lacks specificity as an isolated finding. In the elderly, it is more likely to be secondary to venous insufficiency
   b. Nocturia—due to increased venous return with elevation of legs
   c. Jugular venous distention (JVD)
   d. Hepatomegaly/hepatojugular reflux
   e. Ascites
   f. Right ventricular heave (found with pulmonary HTN)
4. Given enough time, left-sided heart failure can lead to right-sided heart failure (most common cause of right-sided heart failure)
   a. Patients often present with sign/symptoms of both right- and left-sided HF

Quick HIT

Tests to order for a new patient with CHF:
- CBC (anemia)
- BMP (assess for renal injury due to volume overload, or cardiorenal syndrome)
- Cardiac enzymes to rule out MI
- BNP
- CXR (pulmonary edema, cardiomegaly, rule out COPD)
- ECG
- Echocardiogram

C. Diagnosis

1. CXR (Figure 1-8)
   a. Cardiomegaly
   b. *Kerley B lines* are short horizontal lines near periphery of the lung near the costophrenic angles, and indicate pulmonary congestion secondary to dilation of pulmonary lymphatic vessels
   c. Prominent interstitial markings
   d. Pleural effusion
   e. Lung ultrasound can also be used to evaluate for pulmonary edema and pleural effusion
2. Echocardiogram (transthoracic)
   a. Initial test of choice—should be performed whenever CHF is suspected based on history, examination, or CXR
   b. Useful in determining whether systolic or diastolic dysfunction is present, and may help to identify the underlying cause of heart failure
   c. Shows chamber dilation and/or hypertrophy
   d. Evaluates valvular disease
3. B-type natriuretic peptide (BNP) is released from the ventricles in response to ventricular volume expansion and pressure overload
   a. BNP levels >100 pg/mL correlate strongly with the presence of decompensated CHF (unit of measurement varies)
   b. BNP may be useful in differentiating between dyspnea caused by CHF and COPD.

c. N-terminal pro-BNP (NT-proBNP) is a newer assay with similar predictive value as BNP. The normal range for this value depends on the age of the patient, but an NT-proBNP <300 virtually excludes the diagnosis of HF
d. BNP may be falsely low in obese patients

4. ECG is usually nonspecific but can be useful for detecting chamber enlargement and presence of ischemic heart disease or prior MI
5. Radionuclide ventriculography using technetium-99m (“nuclear ventriculography”). Also called multigated acquisition (MUGA) scan
6. Cardiac catheterization can provide valuable quantitative information regarding diastolic and systolic dysfunction, and can clarify the cause of CHF if noninvasive test results are equivocal. Consider coronary angiography to exclude CAD as an underlying cause of CHF
7. Stress testing
   a. Identifies ischemia and/or infarction
   b. Quantifies level of conditioning
   c. Assesses dynamic responses of HR, heart rhythm, and BP

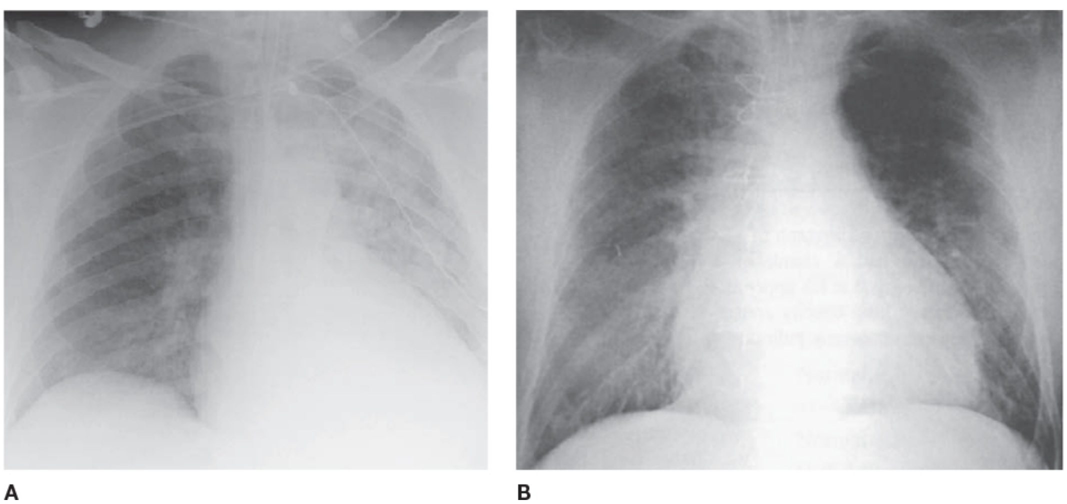


FIGURE 1-8 **A: CXR showing cardiogenic pulmonary edema. B: Another example of cardiogenic pulmonary edema; note cardiomegaly (patient had CHF).**
(**A** reprinted with permission from Mergo PJ. *Imaging of the Chest—A Teaching File.* Lippincott Williams & Wilkins; 2002:50. Figure 24A. **B** reprinted with permission from Stern EJ, White CS. *Chest Radiology Companion*. Lippincott Williams & Wilkins; 1999:38. Figure 5-4.)

Quick HIT

HTN is a common cause of CHF and should be treated. Goal is to reduce preload and afterload.

Quick HIT

The RALES trial showed that spironolactone reduces morbidity and mortality in patients with class III or IV heart failure with EF <35%. It is contraindicated in renal failure (creatinine >2).

Quick HIT

Monitoring a patient with CHF:

- Weight—unexplained weight gain can be an early sign of worsening CHF
- Clinical manifestations (exercise tolerance is key); peripheral edema
- Laboratory values (electrolytes, K, BUN, creatinine levels; serum digoxin level, if applicable)

D. Chronic Treatment

1. HFrEF
   a. General lifestyle modification
   - Sodium restriction (less than 4 g/day)
   - Fluid restriction (1.5 to 2.0 L daily)
   - Weight loss
   - Smoking cessation
   - Restrict alcohol use
   - Exercise program
   - All patients should monitor weight daily to detect fluid accumulation
   - Annual influenza vaccine and pneumococcal vaccine recommended

   b. Diuretics
   - Most effective means of providing *symptomatic* relief to patients with moderate-to-severe CHF.

- Recommended for patients with systolic failure and volume overload.
- Have not been shown to reduce mortality or improve prognosis, just for symptom control. Goal is relief of signs and symptoms of volume overload (dyspnea, peripheral edema).
- Loop diuretics are first line and include furosemide, bumetanide, and torsemide. Furosemide has very inconsistent oral bioavailability compared to bumetanide and torsemide.
- Thiazide-like diuretics: metolazone and chlorothiazide. Used to augment diuresis with loop diuretics.

c. Therapies to improve outcomes: Standard therapy includes the following (medications in parentheses have been shown to improve mortality in HFrEF):
- First-line therapies include ACEi/ARB, ARNI, β-blockers, and hydralazine with a nitrate for those who do not tolerate ACEi/ARB/ARNI
  - ACEi (enalapril, lisinopril, captopril) or ARB (valsartan, losartan, candesartan)
  - β-Blockers (metoprolol succinate, carvedilol, bisoprolol)
  - Primary prevention of sudden cardiac death with ICD implantation if EF <35% on optimal medical therapy
  - Hydralazine and nitrates (isosorbide dinitrate) are an effective combination to reduce afterload in patients with HFrEF who do not tolerate an ACEi/ARB/ARNI. Prior studies showed the greatest benefit in Black patients
  - Sacubitril/valsartan is an angiotensin receptor/neprilysin inhibitor (ARNI) that can be used in patients with EF <35% with maximally tolerated ACEi or ARB, and has been shown to improve mortality (PARADIGM-HF trial)
- Second-line therapies include mineralocorticoid receptor antagonists (MRAs), SGLT2 inhibitors, ivabradine, vericiguat, and digoxin
  - MRAs (spironolactone, eplerenone), if EF <35%
  - SGLT2 inhibitors (dapagliflozin) reduced mortality in the DAPA-HF trial, in HFrEF patients WITH or WITHOUT type 2 DM

- Ivabradine is a funny channel inhibitor that has been shown to reduce hospitalizations in patients with reduced EF and HR >70 on maximally tolerated β-blocker therapy
- Vericiguat is an oral soluble guanylate cyclase simulator that causes vasodilation. It was studied in the VICTORIA trial, which showed a reduction in the composite outcome of death from a cardiovascular cause and first HF hospitalization (though both individual outcomes were nonsignificant)
- Digoxin was once regularly used for HFrEF, but has not been shown to improve mortality. It works as a positive inotropic agent that can provide short-term symptomatic relief. Serum levels should be monitored periodically. Signs of digoxin toxicity include GI (nausea, vomiting, anorexia), cardiac (ectopy, AV block), CNS (visual disturbances, confusion)

Quick HIT

ACE Inhibitors

- Cause venous and arterial dilation, decreasing preload and afterload and thus blood pressure.
- ACEis reduce mortality (Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] and Studies of Left Ventricular Dysfunction [SOLVD] trials), prolong survival, and alleviate symptoms in mild, moderate, and severe HFrEF.
- Monitor BP, potassium, and creatinine.

Quick HIT

Most common cause of death from HF is sudden death from ventricular arrhythmias. Ischemia provokes ventricular arrhythmias.

Quick HIT

Angiotensin II Receptor Blockers (ARBs):

- Can be used in patients unable to take ACEis due to side effect of cough

β-Blockers (specifically metoprolol succinate, carvedilol, and bisoprolol have been shown to reduce mortality):

- Proven to decrease mortality in patients with HFrEF.
- Reported to improve symptoms of HF; may slow progression of heart failure by slowing down tissue remodeling. The decrease in heart rate leads to decreased oxygen consumption.
- β-Blockers have antiarrhythmic, anti-ischemic, and antianginal effect.

Quick HIT

Aldosterone Antagonists (spironolactone, eplerenone)

- Indicated for HFrEF with EF <35%
- Improve all-cause mortality, CV mortality, and hospitalizations
- Can cause hyperkalemia, hence BMP should be monitored (do not start if creatinine >2.5 in men or 2 in women)

A 62-year-old man with a history of hypertension and a myocardial infarction 2 years ago is hospitalized for acute decompensated heart failure. He is diuresed with improvement in symptoms and is discharged on appropriate medications. He is seen in clinic 4 months later with complaints of worsening symptoms over the last month. Previously he became mildly short of breath after significant exertion, but he now reports severe shortness of breath after walking only 50 m. He is asymptomatic only at rest. His current medications include aspirin, sacubitril-valsartan, carvedilol, furosemide, atorvastatin, omega-3 fatty acids, and pantoprazole. An ECG performed in the office shows Q waves in leads V3 and V4, with a normal QRS duration. An echocardiogram performed 1 week ago showed an ejection fraction of 30%.

The patient has been encouraged to quit smoking and drinking alcohol, and to eat a low-sodium diet. What additional therapy is recommended at this time?

A. Lisinopril
B. Spironolactone
C. Cardiac resynchronization therapy
D. Hydralazine and isosorbide dinitrate
E. Both **B** and **C**
F. None of the above

- **The answer is B: Spironolactone.** The patient displays New York Heart Association (NYHA) class III symptoms (no symptoms at rest, but symptoms with minimal exertion). He is on an appropriate initial regimen, which includes a loop diuretic, an angiotensin-neprilysin inhibitor (ARNI), and a β-blocker. The three β-blockers shown to have a survival benefit in heart failure are carvedilol, metoprolol, and bisoprolol. Additional pharmacologic treatment is indicated and includes an aldosterone antagonist (e.g., spironolactone) and a sodium-glucose co-transporter 2 (SGLT2) inhibitor. Notable side

effects of spironolactone include hyperkalemia, gynecomastia, and agranulocytosis. The patient should also consider an ICD given his history of myocardial infarction and reduced ejection fraction. ICDs have been shown to reduce mortality, both for primary prevention and for secondary prevention of fatal arrhythmias. **(A)** The patient is already on an ARNI, which includes an ARB, and there is no benefit to adding an ACE inhibitor. **(C)** Cardiac resynchronization therapy (CRT) may be considered in heart failure patients with dyssynchrony between the left and right ventricles, and therefore criteria for CRT include a QRS duration >120 ms. This patient does not meet criteria. **(D)** Hydralazine and nitrates are used as alternatives to ACE inhibitors and ARBs if the patient cannot tolerate one of these agents.

2. HFpEF: Few therapeutic options available; patients are treated symptomatically *(NO medications have proven mortality benefit)*
   - Diuretics are used for symptom control (volume overload)
   - Patients should continue salt and fluid restriction, take daily weights
   - No other drug classes have been shown to produce significant mortality benefit in randomized controlled trials
3. General principles in treatment of HF (also see Clinical Pearl 1-7)
   a. The following medications should be used with caution in patients with CHF:
      - Metformin—may cause potentially lethal lactic acidosis with renal dysfunction
      - Thiazolidinediones—causes fluid retention
      - NSAIDs may increase risk of CHF exacerbation
      - Some antiarrhythmic agents that have negative inotropic effects
      - CCBs may increase mortality
      - Drugs that can cause hyperkalemia or renal injury
      - Cardiotoxic drugs, such as some chemotherapy drugs

   b. The following devices have been shown to reduce mortality in selected patients:
      - An ICD lowers mortality by helping prevent sudden cardiac death (which is the most common cause of death in CHF). It is indicated

for patients at least 40 days post-MI, EF <35%, and class II or III symptoms despite optimal medical treatment
- Cardiac resynchronization therapy (CRT): This is biventricular pacemaker—indications are similar to ICD except these patients also have prolonged QRS duration >130 ms. Most patients who meet criteria for CRT are also candidates for ICD and receive a combined device

Cardiac transplantation is the last alternative if the above do not control symptoms.

CLINICAL PEARL 1-7

Ventricular Assist Devices in Heart Failure

- **Ventricular assist device (VAD).** Work on these devices has been occurring for the past five decades, and most of the products on the market now represent research that was done 30 years ago. There is great potential for these devices as more research is conducted and clinicians become more experienced in their advantages and drawbacks.
- VADs may be used to support the left ventricle (LVAD), right ventricle (RVAD), or both ventricles (BiVAD).
- The pump is implanted in the **abdominal cavity** with cannulation to the heart. The system controller and battery are worn externally.
- These devices may allow for a patient requiring continuous hospitalization to eventually be discharged with relatively straightforward outpatient follow-up. Patients may live with these devices for a year or more.
- Lifelong anticoagulation with heparin or warfarin is essential without exceptions as these devices are very thrombogenic.
- VADs may also be used for hemodynamic support related to the acute treatment of a STEMI or other cardiac pathology (i.e., while recovering from a severe case of myocarditis).

Quick HIT

The overall 5-year mortality for all patients with CHF is about 50%.

Acute Decompensated Heart Failure

A. Findings

1. Acute dyspnea associated with elevated left-sided filling pressures, with or without pulmonary edema.
2. Most commonly due to LV systolic or diastolic dysfunction.
3. Flash pulmonary edema refers to a severe form of heart failure with rapid accumulation of fluid in the lungs.

B. Diagnosis

1. Differential includes PE, asthma, and pneumonia, all of which can cause rapid respiratory distress.
2. Diagnostic tests include ECG, CXR, ABG, BNP, echocardiogram, and possible coronary angiogram if new onset heart failure and high suspicion for ischemic disease.

C. Treatment

1. Oxygenation and ventilatory assistance with nonrebreather face mask, noninvasive positive pressure ventilation, or even intubation as indicated.
2. Diuretics to treat volume overload and congestive symptoms—this is the most important intervention. Decreases preload.
3. Vasodilators (nitroprusside, nitrates) can be considered in specific patients, such as those with severe HTN or mitral regurgitation.
4. Patients who have pulmonary edema despite use of oxygen, diuretics, and nitrates may benefit from use of inotropic agents (dobutamine). Digoxin takes several weeks to work and is not indicated in an acute setting.
5. Dietary sodium and fluid restriction.
6. Mechanical support devices can be considered in patients with shock.

Arrhythmias

Terminology

- Arrhythmias are typically categorized as whether the QRS complex is narrow or wide (>120 ms).
- Supraventricular tachycardia (SVT) is a broad term that typically refers to tachyarrhythmias with a source above the ventricles (SA node, atria, AV node, His bundle, or a combination of these). SVTs are typically narrow complex, though they can also be wide complex (e.g., SVT with aberrancy).
- The term paroxysmal SVT (PSVT) is often used to describe a subset of SVT that starts and stops abruptly, and are regular. These typically include atrial tachycardia, AV nodal reentrant tachycardia (AVNRT), AV reentrant/reciprocating tachycardia (AVRT).

Premature Complexes

A. Premature Atrial Complexes

1. This early beat arises within the atria, firing on its own.
2. Causes include adrenergic excess, drugs, alcohol, tobacco, electrolyte imbalances, ischemia, hypoxia, and infection.
3. On ECG, look for early P waves that differ in morphology from the normal sinus P wave (because these P waves originate within the atria and not the sinus node).
4. QRS complex is normal because conduction below the atria is normal. There is usually a pause before the next sinus P wave.
5. Premature atrial complexes (PACs) are found in more than 50% of normal adults who undergo Holter monitoring and are of no significance in a normal heart, but may be a precursor of ischemia in a diseased heart.
6. May cause palpitations or give rise to SVT.
7. Usually asymptomatic and do not require treatment. Monitor for increased frequency. If symptomatic (e.g., palpitations), β-blockers may be helpful.

Quick HIT

The Cardiac Arrhythmia Suppression Trial (CAST) I and CAST II studies showed that the use of antiarrhythmic drugs to suppress PVCs after MI increases the risk of death.

Quick HIT

PVCs

- Couplet: Two successive PVCs
- Bigeminy: Sinus beat followed by a PVC
- Trigeminy: Two sinus beats followed by a PVC

B. Premature Ventricular Complexes

1. This early beat fires on its own from a focus in the ventricle and then spreads to the other ventricle.
2. *PVCs can occur in patients with or without structural heart disease.* Causes include hypoxia, electrolyte abnormalities, stimulants, caffeine, medications, and structural heart disease.
3. Since conduction is *not* through normal conduction pathways, but rather through ventricular muscle, it is *slower* than normal, causing a *wide QRS.*
4. Wide, bizarre QRS complexes followed by a compensatory pause are seen; a P wave is not usually seen because it is “buried” within the wide QRS complex.
5. PVCs appear in more than 50% of men who undergo 24-hour Holter monitoring.
6. Most patients are asymptomatic. Some patients may have palpitations and dizziness related to PVCs. If symptomatic, β-blockers may be used.
7. Presence of PVCs in patients with normal hearts is associated with increased mortality.
8. If a patient is found to have frequent PVCs, workup for underlying structural heart disease should be initiated which may require specific treatment.

9. Patients with frequent, repetitive PVCs *and* underlying heart disease are at increased risk for sudden death due to cardiac arrhythmia (especially VFib). Order an electrophysiologic study because patients may benefit from an ICD or ablation.

Quick HIT

Patients with AFib *in the presence of underlying heart disease* have an especially high risk of embolization and hemodynamic compromise.

Tachyarrhythmias

Atrial Fibrillation

A. General Characteristics

1. Multiple foci in the atria fire continuously in a chaotic pattern, causing a totally *irregular, rapid ventricular rate.* Instead of intermittently contracting, the atria quiver continuously.
2. Atrial rate is over 400 bpm, but most impulses are blocked at the AV node so ventricular rate ranges between 75 and 175.
3. Patients with AFib and underlying heart disease are at a markedly increased risk for adverse events, such as thromboembolism and hemodynamic compromise.

B. Causes

1. Heart disease: CAD, MI, HTN, mitral valve disease
2. History of cardiac surgery (scar can predispose to ectopic foci of activity)
3. Pulmonary disease, including PE, COPD, any cause of hypoxia
4. Hyperthyroidism
5. Systemic illness (e.g., sepsis, malignancy)
6. Stress (e.g., postoperative, pain)
7. Excessive alcohol intake ("holiday heart syndrome")

8. Pericarditis
9. Hyperadrenergic states: Pheochromocytoma, cocaine or methamphetamine use
10. Extremes of activity (sedentary lifestyle, excess exercise such as marathon running)

C. Clinical Features

1. Fatigue and exertional dyspnea
2. Palpitations, dizziness, angina, or syncope may be seen
3. An irregularly irregular pulse
4. Blood stasis (secondary to ineffective contraction) leads to formation of intramural thrombi (often in the left atrial appendage), which can embolize to the brain, causing ischemic stroke

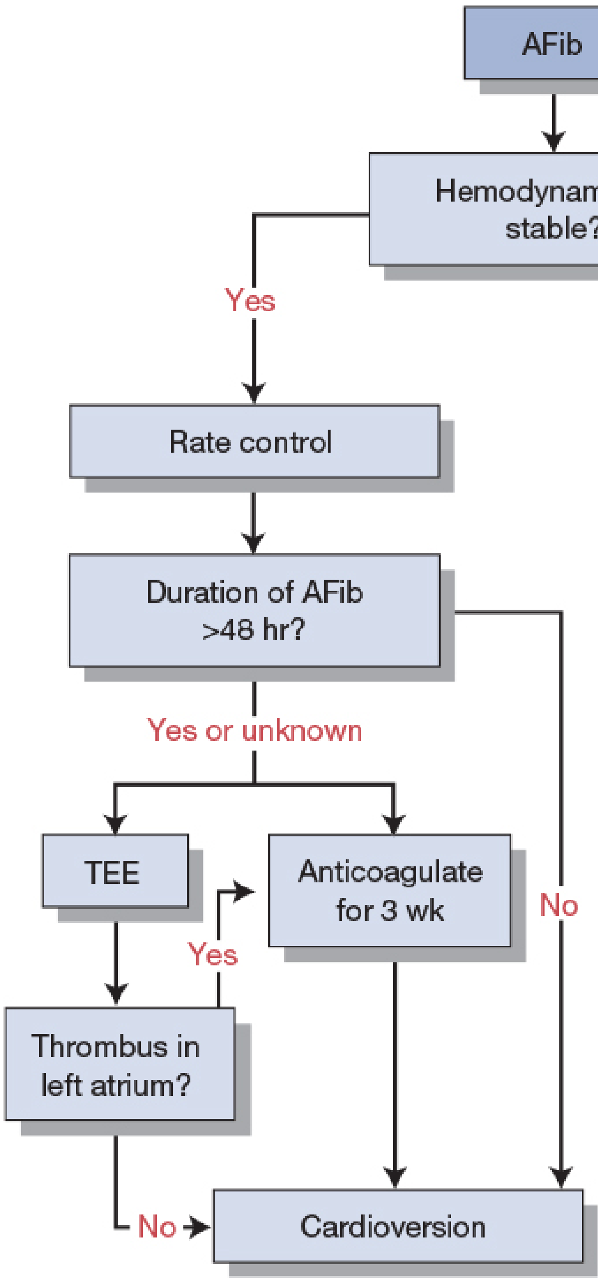


FIGURE 1-9 **Acute management of atrial fibrillation.**

D. Diagnosis

1. ECG findings: Irregularly irregular rhythm (irregular RR intervals and excessively rapid series of tiny, erratic spikes on ECG with a wavy baseline and no identifiable P waves)

Quick HIT

The treatment of AFib and atrial flutter are similar. There are three main goals:

- Rate control: Goal ventricular rate <110
- Assess need for anticoagulation
- Rhythm control: Restore normal sinus rhythm if first presentation or symptomatic

E. Treatment

1. Acute AFib in a hemodynamically *unstable* patient: Immediate electrical cardioversion to sinus rhythm (Figure 1-9; see Clinical Pearl 1-8)
2. Acute AFib in a hemodynamically *stable* patient
   a. Rate control
   - Target heart rate is <110 bpm (lenient rate control was found to be noninferior to strict rate control in the RACE II trial).
   - β-Blockers are preferred agent. CCBs (such as diltiazem) are an alternative if patient does not have HFrEF.
   - If left ventricular systolic dysfunction is present, ideal choice is metoprolol succinate as it will treat both HFrEF and AFib rate control. Can also consider digoxin or amiodarone (useful for rhythm control).

   b. Anticoagulation to prevent cardioembolic cerebrovascular accident (CVA)
   - Risk stratify patients for bleeding complications with the CHA_2DS_2-VASc score.
   - This is a scoring calculator used to estimate annual stroke risk in a patient with AFib or atrial flutter. It assigns 1 point each to presence of heart failure, HTN, age 65 to 74 years, diabetes, female sex, vascular disease, and 2 points each to age >75 years, and history of CVA. The higher the score, the higher the annual stroke risk.
   - For patients with CHA_2DS_2-VASc score >1 (males) or >2 (females), anticoagulation is generally indicated unless high bleeding risk. Because the score includes 1 for being female, there

must be an additional nonsex risk factor for female patients to benefit.

- Choice of anticoagulant depends on etiology of AFib or atrial flutter. For patients with mechanical valves, ventricular assist devices, etc., warfarin should be used. *For other patients, direct oral anticoagulants (DOACs) can be used.*
- DOACs approved for AFib include factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) and direct thrombin inhibitors (dabigatran). These agents do not require lab monitoring.
- An INR of 2 to 3 is the typical anticoagulation goal range for warfarin.
- Acute warfarin-associated bleeding can be reversed with fresh frozen plasma (FFP), prothrombin complex concentrate (PCC).

c. Rhythm control

- Candidates for cardioversion include those who are hemodynamically unstable, those who are symptomatic, and those who are having their first ever case of AFib.
- If rhythm control is selected as a treatment strategy, electrical cardioversion is preferred over pharmacologic cardioversion. Attempts should be made to control ventricular rate before attempting DC cardioversion.
- If AFib present for >48 hours (or unknown period of time), risk of embolization during cardioversion is significant (2% to 5%). Anticoagulate patients for 3 weeks before and at least 4 weeks after cardioversion.
- To avoid waiting 3 weeks for anticoagulation, obtain a transesophageal echocardiogram (TEE) to image the left atrium (LA). If no thrombus is present, start IV heparin and perform cardioversion within 24 hours. Patients still require 4 weeks of anticoagulation after cardioversion.

CLINICAL PEARL 1-8

Cardioversion Versus Defibrillation

Cardioversion

- Delivery of a shock that is **in synchrony** with the QRS complex: Purpose is to terminate certain dysrhythmias such as PSVT or VT; an electric shock during T wave can cause Vfib, so the shock is timed not to hit the T wave.
- Indications: AFib, atrial flutter, VT with a pulse, SVT

Defibrillation

- Delivery of a shock that is **not in synchrony** with the QRS complex: Purpose is to convert a dysrhythmia to normal sinus rhythm.
- Indications: VFib, VT without a pulse.

Automatic Implantable Defibrillator

- Device that is surgically placed: When it detects a lethal dysrhythmia, it delivers an electric shock to defibrillate. It delivers a set number of shocks until the dysrhythmia is terminated.
- Indications: VFib and/or VT that is not controlled by medical therapy.

Quick HIT

The AFFIRM trial showed that rate control is noninferior to rhythm control in treatment of AFib.

Quick HIT

Risk of CVA in patients with AFib. See Table 1-2.

TABLE 1-2 Atrial Fibrillation Annual Stroke Risk

CHA_2DS_2-VASc Score	Annual Stroke Risk (%)
0	Same as general population
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	12.5
9	15.2

3. Chronic AFib
   a. Rate control with a β-blocker or CCB
   b. Atrial fibrillation ablation or chronic rhythm control with an antiarrhythmic medication should be considered in certain patients, thus referral to a cardiologist for evaluation is important
   c. Anticoagulation based on the CHA_2DS_2-VASc score. For elderly patients with falls at home, the risk of embolic stroke (a devastating occurrence) will still likely be much higher than the risk of intracranial bleed from a fall unless there are other significant bleeding risks. Often the decision about chronic anticoagulation is made with the patient after a thorough risks/benefits discussion

A 67-year-old man presents to the hospital with persistent fatigue and some exertional dyspnea. He has a history of hypertension, diabetes, and atrial fibrillation. Cardioversion was attempted previously but without success. His medications include metoprolol, lisinopril, and metformin regularly. On examination, he is normotensive with a heart rate of 76 beats per minute with an irregularly irregular rhythm. There are no murmurs or extra heart sounds, and his lungs are clear to auscultation bilaterally.

Which of the following is the most appropriate next step in management?

A. Repeat cardioversion
B. Aspirin
C. Apixaban
D. Amiodarone

- **The answer is C: Apixaban.** This patient presents with atrial fibrillation and a CHA_2DS_2-VASc score of 3, thus should be on anticoagulation. Although there are other options for anticoagulation (e.g., warfarin), apixaban is the only option listed. **(A)** This patient has chronic atrial fibrillation, and repeat cardioversion may be attempted (since the patient is symptomatic) but only after anticoagulation. **(B)** This patient has a high enough CHA_2DS_2-VASc score to warrant anticoagulation, thus aspirin is not appropriate. **(D)** The patient is on metoprolol with good rate control, thus an antiarrhythmic medication such as amiodarone is not appropriate.

Atrial Flutter

A. General Characteristics

1. Pathophysiology

a. One irritable automaticity focus in the atria fires at about 250 to 350 bpm (typically very close to 300 bpm), giving rise to regular atrial contractions.
b. Atrial rate between 250 and 350, around 300 bpm. The long refractory period in the AV node allows only one out of every two or three flutter waves to conduct to the ventricles.

2. Causes
   a. Heart disease: Heart failure (most common association), rheumatic heart disease, CAD
   b. COPD, other hypoxic pulmonary disease
   c. Atrial septal defect (ASD)
   d. Very similar risk factors to AFib

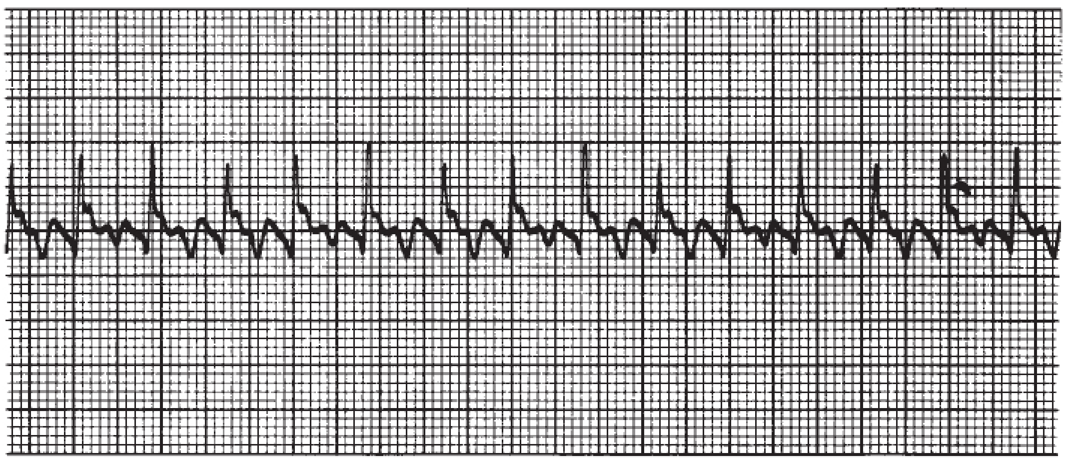


FIGURE 1-10 **Atrial flutter.**
(Reprinted with permission from Nettina SM. *The Lippincott Manual of Nursing Practice*. 9th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:431. Figure 13-12.)

B. Diagnosis

1. ECG provides a **saw-tooth** baseline, with a QRS complex appearing after every second or third "tooth" (P wave). Saw-tooth flutter waves are best seen in the inferior leads (II, III, aVF) (Figure 1-10).

C. Treatment

1. Same general treatment strategies as AFib

2. However, atrial flutter ablation is highly successful and can be used to avoid long-term anticoagulation if risk factors present

Multifocal Atrial Tachycardia

- Usually occurs in patients with severe pulmonary disease (e.g., COPD).
- ECG findings: Variable P-wave morphology and variable PR and RR intervals. At least three different P-wave morphologies are required to make an accurate diagnosis.
- The diagnosis of *wandering atrial pacemaker* is identical except that the heart rate is between 60 and 100 bpm (i.e., not tachycardic).
- Can also be diagnosed by use of vagal maneuvers or adenosine to show AV block without disrupting the atrial tachycardia.
- Treatment directed at the underlying disease, improving oxygenation and ventilation (strong association between MAT and lung disease). If left ventricular function is preserved, acceptable treatments include CCBs, β-blockers, digoxin, amiodarone, IV flecainide, and IV propafenone. If LV function is not preserved, use digoxin, diltiazem, or amiodarone. Electrical cardioversion is ineffective and should not be used.

Paroxysmal Supraventricular Tachycardia

A. General Characteristics

1. Pathophysiology (most often due to reentry)
   a. Atrial tachycardia
      - Ectopic focus outside of the sinus node with a constant rate >100 bpm.
      - Can be incessant (>90% of the time while the patient is monitored), caused by medications (e.g., digoxin toxicity), or caused by a variety of other drugs/toxins and systemic conditions.

   b. AVNRT
      - Two pathways (one fast and the other slow) *within the AV node*, so the reentrant circuit is within the AV node
      - Initiated or terminated by PACs

- ECG: *Narrow QRS complexes* with no discernible P waves (P waves are buried within the QRS complex). This is because the circuit is short and conduction is rapid, so impulses exit to activate atria and ventricles simultaneously. Can sometimes have *retrograde P waves*, or P waves which occur *after* QRS complex

c. AV reentrant tachycardia (AVRT)

- An accessory pathway between the atria and ventricles that conducts antegrade or retrograde
- Orthodromic AVRT (more common): results in a narrow complex tachycardia. A premature beat (PAC or PVC) causes a fast loop that travels through the AV node and His–Purkinje system to the ventricles, then cycles back to the atria through the accessory pathway to continue the cycle
- Antidromic AVRT (less common): results in a wide complex tachycardia. Also initiated by a premature beat but the direction of the cycle is reversed, where the impulse travels from the atria to the ventricle via the accessory pathway, then retrograde from the ventricles to the His–Purkinje system, AV node, and back to the atria

Quick HIT

In accordance with the electrical conducting system of the heart (SA node, atria, AV node, bundle of His, bundle branches, Purkinje fibers), tachycardias can be quickly separated into two categories based on the width of the QRS complex.

- Narrow QRS complexes suggest that the arrhythmia originates at or above the level of the AV node.
- Wide QRS complexes suggest that the arrhythmia originates outside of the normal conducting system or there is a supraventricular arrhythmia with coexisting abnormality in the His–Purkinje system.

Quick HIT

Side Effects of Adenosine

- Headache
- Flushing
- SOB
- Chest pressure
- Nausea
- Sense of doom

B. Treatment

1. Maneuvers that stimulate the vagus nerve delay AV conduction and thus block the reentry mechanism: The Valsalva maneuver, carotid sinus massage, breath holding, and head immersion in cold water (or placing an ice bag to the face)
2. Acute treatment
   a. Pharmacologic therapy
      - *IV adenosine—agent of choice* due to short duration of action; works by inhibiting AV nodal activity. Is used both as diagnostic (to see underlying atrial rhythm) and therapeutic agent (to terminate certain SVTs such as AVNRT and AVRT).
      - IV diltiazem (CCB) and IV metoprolol (β-blocker) or digoxin are alternatives in patients with preserved left ventricular function.
      - DC cardioversion if drugs are not effective or if unstable; almost always successful.
3. Prevention
   a. Pharmacologic therapy: CCBs or β-blockers
   b. Radiofrequency catheter ablation of either the AV node or the accessory tract (depending on which is the accessory pathway) is preferred if episodes are recurrent and symptomatic

Wolff–Parkinson–White (WPW) Syndrome

A. General Characteristics

1. An accessory conduction pathway from atria to ventricles through the bundle of Kent causes premature ventricular excitation because it lacks the delay seen in the AV node.
2. May lead to a PSVT, more commonly orthodromic AVRT than antidromic AVRT.
3. Patients with WPW can also present with AVNRT, atrial fibrillation, atrial flutter, ventricular tachycardia, and VFib.

B. Diagnosis

1. ECG: Narrow complex tachycardia, a short PR interval (usually <100 ms), and a delta wave (upward deflection seen before the QRS complex)

C. Treatment

1. Radiofrequency catheter ablation of one arm of the reentrant loop (i.e., of the accessory pathway) is an effective treatment. Medical options include procainamide or quinidine.
2. Avoid drugs active on the AV node (e.g., digoxin, CCBs, β-blockers, adenosine) because they may accelerate conduction through the accessory pathway, resulting in VFib. Type IA antiarrhythmics (i.e., procainamide) are better choices, as they will suppress conduction through the accessory pathway instead.

Quick HIT

VT or VFib causes 75% of episodes of cardiac arrest.

Summary of Atrial Tachyarrhythmias (Figure 1-11)

Ventricular Tachycardia

A. General Characteristics

1. Defined as rapid and repetitive firing of three or more PVCs in a row, at a rate of between 100 and 250 bpm
2. AV dissociation is present, that is, sinus P waves continue with their cycle, unaffected by the tachycardia
3. Originates below the bundle of His
4. Causes
   a. CAD with prior MI is the most common cause
   b. Active ischemia, hypotension
   c. Cardiomyopathies, especially those with infiltration into myocardium such as sarcoidosis
   d. Ventricular scar tissue
   e. Congenital defects
   f. Long QT syndrome (results in torsades de pointes)
   g. Drug toxicity

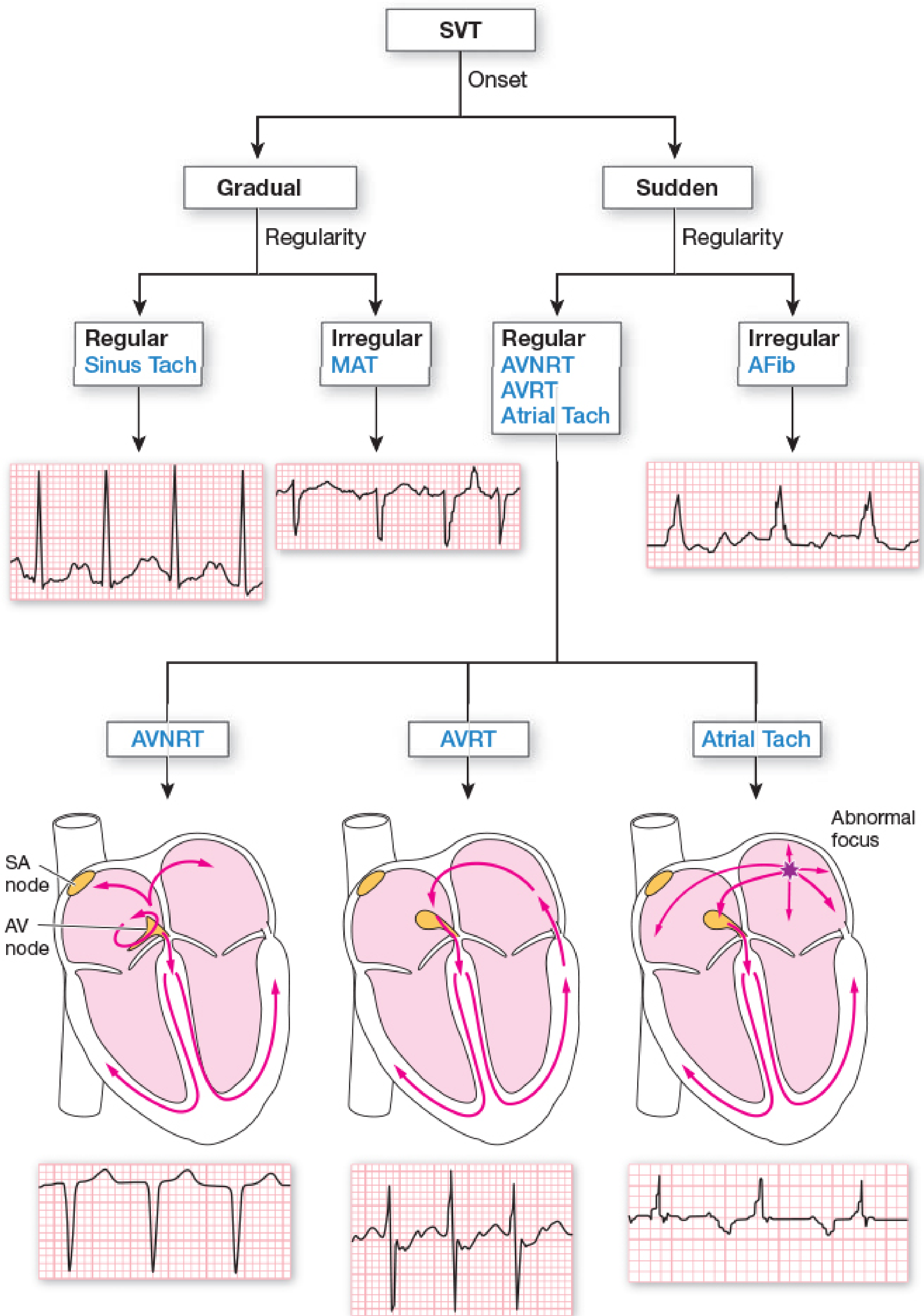


FIGURE 1-11 **Atrial arrhythmias. AV, atrioventricular; AVNRT, AV nodal reentry tachycardia; AVRT, AV reentry tachycardia; MAT, multifocal tachycardia; SA, sinoatrial; SVT, supraventricular tachyarrhythmias.**

(Reprinted with permission from Jackson KP, Daubert JP. Supraventricular tachyarrhythmias. In: Strauss DG, Schocken DD, eds. *Marriott's Practical Electrocardiography.* 13th ed. Wolters Kluwer; 2022:321–344. Summary Illustration 15-1.)

5. Sustained versus nonsustained VT
   a. Sustained VT (persists in the absence of intervention)
      - Lasts longer than 30 seconds and is often symptomatic
      - Can be associated with marked hemodynamic compromise (i.e., hypotension) and/or development of myocardial ischemia
      - A life-threatening arrhythmia
      - Can progress to VFib if untreated
   b. Nonsustained VT
      - Brief, self-limited runs of VT
      - Usually asymptomatic
      - When CAD and LV dysfunction are present, it is an independent risk factor for sudden death. Therefore, patients with nonsustained VT should be thoroughly evaluated for underlying CAD and LV dysfunction
6. *Torsades de pointes* is a rapid polymorphic VT. It is a dangerous arrhythmia that often can lead to VFib.
   - It is associated with many factors that prolong the QT interval.
   - Risk factors for long QT include: electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), drugs (e.g., antiemetics, antipsychotics, SSRIs, TCAs, macrolide and fluoroquinolone antibiotics, many others), and congenital long QT syndrome.
   - IV *magnesium* provides cardiac stabilization.
   - Electrical cardioversion for unstable patients. May require drugs to increase heart rate such as isoproterenol to shorten QT interval while underlying cause is addressed.
   - Address the underlying cause.
7. Prognosis depends on the presence of CAD and on whether VT is sustained or nonsustained. VT after an MI usually has a poor prognosis, especially if it is sustained. In patients with no underlying heart condition, the prognosis is good.

B. Clinical Features of VT

1. Palpitations, dyspnea, lightheadedness, angina, impaired consciousness (syncope or near-syncope)
2. May present with sudden cardiac death
3. Signs of cardiogenic shock may be present
4. May be asymptomatic if rate is slow
5. Physical findings include *cannon A waves* in the neck (secondary to AV dissociation, which results in atrial contraction during ventricular contraction) and an S1 that varies in intensity

Quick HIT

Always suspect VT in a patient with a wide (>0.12 second) QRS tachycardia.

C. Diagnosis

1. ECG: Wide and bizarre QRS complexes (Figure 1-12).
2. QRS complexes may be mono- or polymorphic
   a. In monomorphic VT, all QRS complexes are identical
   b. In polymorphic VT, the QRS complexes are different
3. Unlike PSVT, VT does not respond to vagal maneuvers or adenosine

D. Treatment

1. Identify and treat reversible causes
2. Sustained VT
   a. Hemodynamically stable patients with mild symptoms and systolic BP >90—pharmacologic therapy
      - Advanced cardiac life support (ACLS) guidelines recommend IV amiodarone
   b. Hemodynamically unstable patients or patients with severe symptoms
      - Immediate synchronous DC cardioversion
      - Follow with IV amiodarone to maintain sinus rhythm
   c. Ideally, all patients with sustained VT should undergo placement of an ICD, unless EF is normal (then consider amiodarone)
3. Nonsustained VT

a. If no underlying heart disease and asymptomatic, do not treat. These patients are *not* at increased risk of sudden death.
b. If the patient has underlying heart disease, a recent MI, evidence of left ventricular dysfunction, or is symptomatic, order an electrophysiologic study: If it shows inducible, sustained VT, ICD placement is appropriate.
c. Pharmacologic therapy is second-line treatment. However, amiodarone has the best results of all of the antiarrhythmic agents.

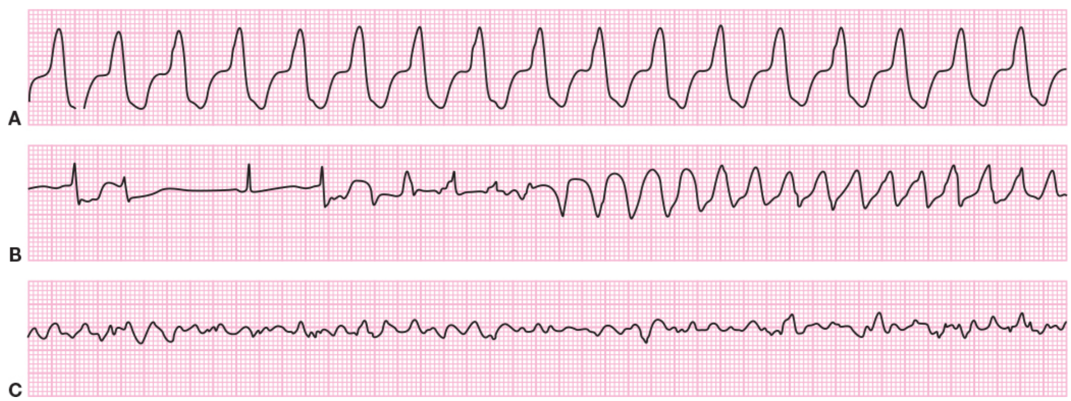


FIGURE 1-12 Different types of ventricular tachyarrhythmias. (A) Monomorphic ventricular tachycardia characterized by a wide QRS complex rhythm, rate greater than 100 bpm, with the same beat-to-beat electrocardiographic (ECG) morphology. (B) Polymorphic ventricular tachycardia with beat-to-beat variability in QRS morphology. Prolonged QT interval can be appreciated at the beginning of the rhythm strip, which predisposes to torsades de pointes. (C) Ventricular fibrillation with disorganized, irregular electrical activity at a rate greater than 300 bpm.

(Reprinted with permission from Hayase J, Bradfield JS. Ventricular tachycardia. In: Mukherjee D, Lange RA, Bailey S, et al., eds. *Cardiovascular Medicine and Surgery*. Wolters Kluwer; 2021:620. Figure 57.1.)

***Quick* HIT**

- It is important to distinguish monomorphic VT from SVT with aberrant conduction.
- Wide complex tachycardia in adults with a history of structural heart disease is much more likely to be due to VT than SVT with aberrancy.

Quick HIT

If a patient with underlying heart disease is found to have nonsustained VT, an implantable defibrillator has been shown to be the most effective treatment.

Ventricular Fibrillation

A. General Characteristics

1. Multiple foci in the ventricles fire rapidly, leading to a chaotic quivering of the ventricles and no cardiac output
2. Most episodes of VFib begin with VT (except in the setting of acute ischemia/infarction)
3. Recurrence
   a. If VFib is not associated with acute MI, recurrence rate is high (up to 30% within the first year). These patients require chronic therapy: Either prophylactic antiarrhythmic therapy (amiodarone) or implantation of an ICD.
   b. If VFib develops within 48 hours of an acute MI, long-term prognosis is favorable and the recurrence rate is low (2% at 1 year). Chronic therapy is not required in these patients.
4. Fatal if untreated

Quick HIT

Cardiac arrest and sudden cardiac death are not synonymous:

Cardiac arrest: Sudden loss of cardiac output; potentially reversible if circulation and oxygen delivery are promptly restored.

Sudden cardiac death: Unexpected death within 1 hour of symptom onset secondary to a cardiac cause.

B. Causes

1. Ischemic heart disease is the most common cause
2. Antiarrhythmic drugs, especially those that cause torsades de pointes (prolonged QT intervals)

3. AFib with a very rapid ventricular rate in patients with Wolff–Parkinson–White (WPW) syndrome

C. Clinical Features

1. Cannot measure BP; absent heart sounds and pulse
2. Patient is unconscious
3. If untreated, leads to eventual sudden cardiac death

D. Diagnosis

1. ECG: No atrial P waves can be identified
2. No QRS complexes can be identified
3. In sum, no waves can be identified; there is a very irregular rhythm

Quick HIT

- Drugs cannot convert VFib by themselves. Defibrillation is key, along with CPR and epinephrine.
- Defibrillation does not work for asystole. Perform CPR and administer epinephrine.

E. Treatment

1. This is a medical emergency!
   a. Follow the ACLS algorithm, which involves early defibrillation, CPR, epinephrine, followed eventually by a trial of amiodarone or lidocaine.
2. If cardioversion is successful:
   a. Maintain continuous IV infusion of the effective antiarrhythmic agent. IV amiodarone has been shown to be effective.
   b. Implantable defibrillators have become the mainstay of chronic therapy in patients at continued risk for VF. Long-term amiodarone therapy is an alternative.

Quick HIT

Pulseless Electrical Activity (PEA)

- Occurs when electrical activity is on the monitor but there are no pulses (even with Doppler), and carries a grim prognosis.
- Treat possible causes (hypoxia, hypovolemia, hypotension, hyperkalemia, acidosis, tamponade, tension pneumothorax, toxins, PE, MI) and medicate according to ACLS guidelines.

Bradyarrhythmias

Sinus Bradycardia

- Sinus rate <60 bpm
- Causes include ischemia, increased vagal tone, antiarrhythmic drugs; may be a normal finding in trained athletes
- Can be asymptomatic; patients may complain of fatigue, inability to exercise, angina, or syncope
- Atropine can elevate the sinus rate by blocking vagal stimulation to the sinoatrial node. A cardiac pacemaker may be required if bradycardia persists with symptoms or syncope

Sick Sinus Syndrome

- Sinus node dysfunction characterized by a persistent spontaneous sinus bradycardia. Patients usually elderly.
- Symptoms include dizziness, confusion, syncope, fatigue, and CHF.
- Pacemaker implantation may be required (see Clinical Pearl 1-9).

CLINICAL PEARL 1-9

Cardiac Pacemakers

1. Device that delivers direct electrical stimulation to the heart when the heart's natural pacemaker is unable to do so
2. There are three types:
   - Permanent implantable system for long-term treatment
   - Temporary systems—either transcutaneous (with electrode pads over chest) or transvenous—both use an external pulse generator that patient can secure to the waist with straps
3. On ECG, cardiac pacing is noted by the presence of a "spike."
4. Indications
   - Sinus node dysfunction is the most common indication
   - Symptomatic heart block—Mobitz II second-degree block and complete heart block (even if asymptomatic)
   - Symptomatic bradyarrhythmias
   - Tachyarrhythmias to interrupt rapid rhythm disturbances

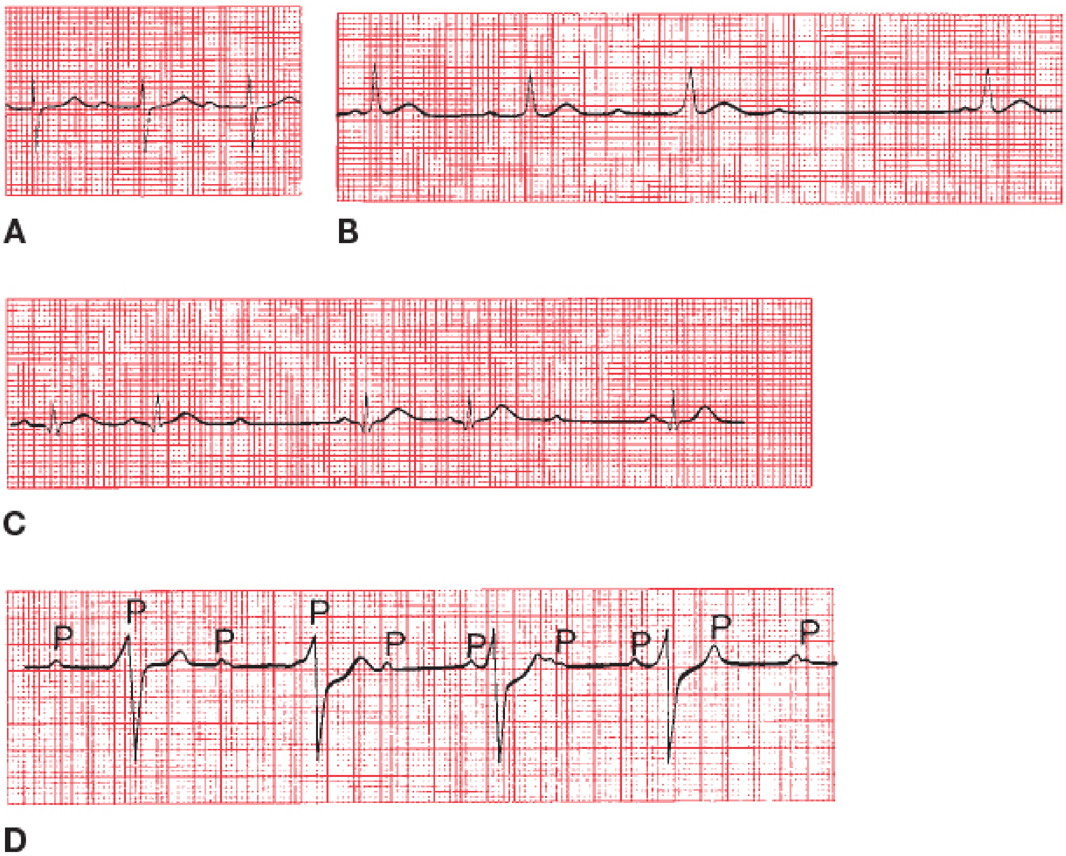


FIGURE 1-13 **Atrioventricular (AV) block. (A) First-degree AV block. (B) Mobitz type 1 second-degree AV block (Wenckebach block). (C) Mobitz type 2 second-degree AV block. (D) Third-degree AV block.**
(Reprinted with permission from Thaler M. Putting it all together. In: Thaler M, ed. *The Only EKG Book You'll Ever Need*. 9th ed. Wolters Kluwer; 2019:340. UNFigure 8-12.)

Quick HIT

Second-degree Mobitz type II and third-degree AV blocks require pacemaker implantation.

AV Block

A. First-Degree AV Block

1. PR interval is prolonged (>0.20 second) (Figure 1-13).

2. A QRS complex follows each P wave.
3. Delay is usually in the AV node.
4. Benign condition that does not require treatment.

B. Second-Degree AV Block (Includes Mobitz Types I and II)

1. Mobitz type I (Wenckebach)
   a. Characterized by progressive prolongation of PR interval until a P wave fails to conduct
   b. Site of block is usually within the AV node
   c. Benign condition that does not require treatment
2. Mobitz type II
   a. P wave fails to conduct suddenly, without a preceding PR interval prolongation; therefore, the QRS drops suddenly
   b. Often progresses to third-degree AV block
   c. Site of block is within the His–Purkinje system
   d. **Pacemaker** implantation is necessary

C. Third-Degree (Complete) AV Block

1. Absence of conduction of atrial impulses to the ventricles; no correspondence between P waves and QRS complexes
2. A ventricular pacemaker (escape rhythm) maintains a ventricular rate of 25 to 40 bpm
   a. Characterized by **AV dissociation**
   b. **Pacemaker** implantation is necessary

Diseases of the Heart Muscle

Dilated Cardiomyopathy

- Characterized by biventricular dilation and impaired systolic function.
- There is a long list of causes, including viral and genetic. See HFrEF section for evaluation and management.

Hypertrophic Cardiomyopathy

A. General Characteristics

1. Most cases are inherited as an **autosomal-dominant** trait. However, spontaneous mutations may account for some cases.
2. Pathophysiology
   a. The main problem is diastolic dysfunction due to a stiff, hypertrophied ventricle with elevated diastolic filling pressures.
   b. These pressures increase further with factors that increase HR and contractility (such as exercise) or decrease left ventricular filling (e.g., the Valsalva maneuver).
   c. Patients may also have a dynamic outflow obstruction due to asymmetric hypertrophy of the interventricular septum.

B. Clinical Features

1. Symptoms
   a. Dyspnea on exertion
   b. Chest pain (angina)
   c. Syncope (or dizziness) after exertion or the Valsalva maneuver
   d. Palpitations
   e. Arrhythmias (AFib, ventricular arrhythmias)—due to persistently elevated atrial pressures
   f. Cardiac failure due to increased diastolic stiffness
   g. Sudden death—sometimes seen in a young athlete; may be the first manifestation of disease
   h. Some patients may remain asymptomatic for many years
2. Signs
   a. Sustained PMI
   b. Loud S_4
   c. Systolic ejection murmur
      - Decreases with squatting, lying down, or straight-leg raise (due to decreased outflow obstruction)
      - Intensity increases with Valsalva and standing (decreases LV size and thus increases the outflow obstruction)
      - Decreases with sustained handgrip (increased systemic resistance leads to decreased gradient across aortic valve)

- Best heard at left lower sternal border (LLSB)

d. Rapidly increasing carotid pulse with two upstrokes (bisferious pulse)

Quick HIT

- Standing, the Valsalva, and leg raise maneuvers diminish the intensity of all murmurs except MVP and hypertrophic cardiomyopathy (HCM). These maneuvers decrease left ventricular volume.
- Squatting increases the intensity of all murmurs except MVP and HCM.
- Sustained handgrip diminishes the intensity of HCM murmur. Sustained handgrip increases systemic resistance.

C. Diagnosis

1. Echocardiogram establishes the diagnosis
2. Clinical diagnosis and family history

D. Treatment

1. Asymptomatic patients generally do not need treatment, but this is controversial. No studies have shown any alteration in the prognosis with therapy, so treatment generally focuses on reducing symptoms.
2. All patients should avoid strenuous exercise, including competitive athletics.
3. Symptomatic patients should use negatively inotropic drugs.
   a. β-Blockers should be the initial drug used in symptomatic patients; they reduce symptoms by improving diastolic filling (as HR decreases, duration in diastole increases), and also reduce myocardial contractility and thus oxygen consumption.
   b. CCBs (verapamil or another non-DHP CCB).
      - Can be used if patient is not responding to β-blocker.
      - Reduce symptoms by similar mechanism as β-blockers.
   c. Disopyramide can be added to either β-blocker or CCB to improve symptoms.
   d. Diuretics: Use with caution, as they can cause volume depletion, leading to LV outflow tract obstruction.
   e. If AFib is present, treat accordingly (see Atrial Fibrillation).
   f. Surgery

- Alcohol septal ablation is a less invasive procedure than myomectomy that can lower the bulk of the interventricular septum and relieve obstructive symptoms.
- Myomectomy has a high success rate for relieving symptoms. It involves the excision of part of the myocardial septum. It is reserved for patients with severe disease.
- Mitral valve replacement is now rarely performed. Repair sometimes performed at the time of surgical myomectomy.

Restrictive Cardiomyopathy

A. General Characteristics

1. Infiltration of the myocardium results in impaired diastolic ventricular filling due to decreased ventricular compliance.
2. Systolic dysfunction is variable and usually occurs in advanced disease.
3. Less common than dilated and hypertrophic cardiomyopathies.

B. Causes of Restrictive Cardiomyopathy

1. Amyloidosis
2. Sarcoidosis
3. Hemochromatosis
4. Scleroderma
5. Carcinoid syndrome
6. Chemotherapy or radiation induced
7. Idiopathic

C. Clinical Features

1. Elevated filling pressures cause dyspnea and exercise intolerance.
2. Right-sided signs and symptoms are present for the same reason.

D. Diagnosis

1. Echocardiogram
   a. Thickened myocardium and possible systolic ventricular dysfunction

b. Increased right atrium (RA) and LA size with normal LV and RV size
c. In amyloidosis, myocardium appears brighter or may have a speckled appearance

2. ECG: Low voltages or conduction abnormalities, arrhythmias, AFib
3. Endomyocardial biopsy may be diagnostic

E. Treatment

1. Treat underlying disorder
   a. Hemochromatosis: Phlebotomy or deferoxamine
   b. Sarcoidosis: Glucocorticoids for acute flares
   c. Amyloidosis: Treat underlying cause of amyloidosis, consider organ transplantation if severe end-organ disease (i.e., heart, kidney, liver if transthyretin amyloidosis)
   d. Treat according to EF (HFrEF therapy or HFpEF therapy)
2. Use diuretics and vasodilators (for pulmonary and peripheral edema) cautiously, because a decrease in preload may compromise cardiac output

Myocarditis

- Inflammation of the myocardium, with many possible causes, including viruses (e.g., Coxsackie, parvovirus B19, human herpes virus 6), bacteria (group A streptococcus in rheumatic fever, Lyme disease, mycoplasma, etc.), SLE, medications (e.g., sulfonamides); can also be idiopathic.
- May be asymptomatic, or may present with fatigue, fever, chest pain, pericarditis, CHF, arrhythmia, or even death.
- Look for elevations in cardiac enzyme levels and erythrocyte sedimentation rate.
- Treatment is supportive. Treat underlying causes if possible, and treat any complications.

Pericardial Diseases

Acute Pericarditis

A. General Characteristics

1. Inflammation of the pericardial sac—may be an isolated finding or part of an underlying disorder or generalized disease
2. Causes
   a. Idiopathic (probably postviral): Most cases of idiopathic pericarditis are presumed to be postviral, usually preceded by a recent flu-like illness or by upper respiratory or GI symptoms
   b. Infectious: Viral (e.g., Coxsackievirus, echovirus, adenovirus, EBV, influenza, HIV, hepatitis A or B), bacterial (tuberculosis), fungal, toxoplasmosis
   c. Acute MI (first 24 hours after MI)
   d. Uremia
   e. Collagen vascular diseases (e.g., SLE, scleroderma, rheumatoid arthritis, sarcoidosis)
   f. Neoplasm—especially Hodgkin lymphoma, breast, and lung cancers
   g. Drug-induced lupus syndrome (procainamide, hydralazine)
   h. After MI: (*Dressler syndrome*)—usually weeks to months after MI
   i. After surgery—postpericardiotomy syndrome
   j. Amyloidosis
   k. Radiation
   l. Trauma
3. The majority of patients recover within 1 to 3 weeks. A minority of patients have a prolonged course or recurrent symptoms
4. Complications
   a. Pericardial effusion
   b. Cardiac tamponade—can occur in up to 15% of patients; close observation is important

Quick HIT

Diagnostic criteria of acute pericarditis (need at least 2/4):

- Classic pleuritic chest pain with positional component
- Pericardial friction rub
- ECG changes—diffuse ST elevations; PR depression, PR elevation in aVR
- Pericardial effusion (seen on CXR or echocardiogram)

B. Clinical Features

1. Chest pain (most common finding)
   a. Often severe and *pleuritic*
   b. Often localized to the retrosternal and left precordial regions and radiates to the trapezius ridge and neck
   c. Pain is *positional:* It is aggravated by lying supine, coughing, swallowing, and deep inspiration. *Pain is relieved by sitting up and leaning forward*
   d. Pain is not always present, depending on the cause (e.g., usually absent in rheumatoid pericarditis)
2. Fever and leukocytosis may be present
3. Patient may give symptoms of preceding viral illness such as a nonproductive cough or diarrhea
4. Pericardial friction rub
   a. Not always present, but it is very specific for pericarditis
   b. Caused by friction between visceral and parietal pericardial surfaces
   c. Scratching, high-pitched sound with up to three components. Patients may have any or all of the three components:
      - Atrial systole (presystolic)
      - Ventricular systole (loudest and most frequently heard)
      - Early diastole
   d. Heard best during expiration with patient sitting up and with stethoscope placed firmly against the chest
   e. Friction rub may come and go over a period of several hours, and can vary greatly in intensity

C. Diagnosis

1. **ECG** shows four changes in sequence
   a. Diffuse ST elevation and PR depression, with PR elevation in lead aVR
   b. ST segment returns to normal—typically around 1 week
   c. T-wave inverts—does not occur in all patients
   d. T wave returns to normal
2. Echocardiogram if pericarditis with effusion is suspected

D. Treatment

1. Most cases are self-limited and resolve in 2 to 6 weeks.
2. Treat the underlying cause if known.
3. First-line therapy is high-dose NSAIDs (aspirin, ibuprofen, naproxen, or indomethacin). Colchicine is recommended as adjunctive therapy in addition to NSAIDs.
4. Glucocorticoids may be tried if pain does not respond to NSAIDs, but should be avoided if at all possible, as they are associated with a high rate of recurrent pericarditis.
5. Relatively uncomplicated cases can be treated as an outpatient. However, patients with more worrisome symptoms such as fever and leukocytosis and patients with worrisome features such as pericardial effusion should be hospitalized.

Constrictive Pericarditis

A. General Characteristics

1. *Fibrous scarring of the pericardium* leads to rigidity and thickening of the pericardium, with obliteration of the pericardial cavity.
2. Pathophysiology
   a. A fibrotic, rigid pericardium restricts the diastolic filling of the heart.
   b. Ventricular filling is unimpeded during early diastole because intracardiac volume has not yet reached the limit defined by the stiff pericardium.
   c. When intracardiac volume reaches the limit set by the noncompliant pericardium, ventricular filling is halted abruptly. (In contrast,

ventricular filling is impeded throughout diastole in cardiac tamponade.)

3. Causes
   a. In most patients, the cause is never identified and is idiopathic or related to a previous viral infection.
   b. Other causes include recurrent pericarditis, uremia, radiation therapy, tuberculosis, chronic pericardial effusion, tumor invasion, connective tissue disorders, and prior surgery involving the pericardium.

Quick HIT

Diastolic Dysfunction in Constrictive Pericarditis

Early diastole: Rapid filling
Late diastole: Halted filling

Quick HIT

If a patient has clinical signs of cirrhosis (ascites, hepatomegaly) and distended neck veins, perform tests to rule out constrictive pericarditis.

B. Clinical Features

1. Patients appear very ill
2. Patients with constrictive pericarditis typically present in one of the two ways:
   a. With symptoms characteristic of fluid overload such as edema, ascites, and pleural effusions.
   b. With symptoms related to the diminished cardiac output such as dyspnea on exertion, fatigue, decreased exercise tolerance, and cachexia.
   c. Patient can present with a combination of both of these findings.
3. Signs include:
   a. JVD—most prominent physical finding; central venous pressure (CVP) is elevated and displays prominent x and y descents
   b. *Kussmaul sign*—JVP (venous pressure) paradoxically increases during inspiration

c. Pericardial knock—corresponding to the abrupt cessation of ventricular filling
d. Ascites
e. Dependent edema

4. May be difficult to distinguish from restrictive cardiomyopathy—may require echo or cardiac catheterization to distinguish these entities

Quick HIT

Often, constrictive pericarditis progresses to worsening cardiac output and to hepatic and/or renal failure. Surgical treatment (pericardiectomy) is indicated in many cases, but has high risk of morbidity and mortality.

Quick HIT

Echocardiogram is the imaging study of choice for diagnosis of pericardial effusion and cardiac tamponade physiology (has a high sensitivity).

C. Diagnosis

1. ECG
   a. Nonspecific changes such as low QRS voltages, generalized T-wave flattening or inversion, left atrial abnormalities.
   b. **AFib** is more often seen in advanced disease but overall occurs in fewer than half of all patients.
2. Echocardiogram
   a. Increased pericardial thickness is seen in about half of all patients.
   b. A sharp halt in ventricular diastolic filling and atrial enlargement can also be seen.
3. CT scan and MRI may also show pericardial thickening and calcifications, and can aid greatly in the diagnosis.
4. Cardiac catheterization
   a. Elevated and equal diastolic pressures in all chambers.
   b. Ventricular pressure tracing shows a rapid y descent, which has been described as a dip and plateau or a "square root sign."

D. Treatment

1. Treat the underlying condition
2. Diuretics may be extremely helpful in treating fluid overload symptoms
3. Surgical pericardiectomy

Quick HIT

Pericardial effusion is important clinically when it develops rapidly because it may lead to cardiac tamponade.

Pericardial Effusion

A. General Characteristics

1. Excess fluid in the space between the heart and the pericardium.
2. Can be acute or chronic. Acute effusions are more likely to result in tamponade.
3. Caused by a long list of etiologies, with many cases being idiopathic. Other categories include volume overload states, malignant, iatrogenic, infectious, and associated with autoimmune/inflammatory conditions.

B. Clinical Features

1. All physical examination signs are extremely nonspecific and often do not aid in the diagnosis but may include:
   a. Muffled heart sounds
   b. Soft PMI
   c. Dullness at left lung base (because it may be compressed by pericardial fluid)
   d. Pericardial friction rub may or may not be present

C. Diagnosis

1. Echocardiogram
   a. Imaging procedure of choice: Confirms the presence or absence of a significant effusion

b. Most sensitive and specific method of determining whether pericardial fluid is present; can show as little as 20 mL of fluid
c. Should be performed in all patients with acute pericarditis to rule out an effusion
2. CXR
a. CXR shows enlargement of cardiac silhouette when >250 mL of fluid has accumulated
b. Cardiac silhouette may have prototypical "water bottle" appearance
c. An enlarged heart without pulmonary vascular congestion suggests pericardial effusion
3. ECG
a. May show low QRS voltages and T-wave flattening but should not be used to diagnose pericardial effusion
b. Electrical alternans (see definition below under Cardiac Tamponade) suggests a massive pericardial effusion and tamponade
4. CT scan or MRI—very accurate, but often unnecessary given the accuracy of an echocardiogram
5. Pericardial fluid analysis—may clarify the cause of the effusion
a. Order protein and glucose content, cell count and differential, cytology, specific gravity, hematocrit, Gram stain, acid-fast stains, mycobacterial PCR, fungal smear, cultures, LDH content

D. Treatment

1. Depends on patient's hemodynamic stability.
2. Pericardiocentesis is not indicated unless there is evidence of cardiac tamponade. Analysis of pericardial fluid can be useful if the cause of the effusion is unknown.
3. If the effusion is small and clinically insignificant, a repeat echocardiogram in 1 to 2 weeks is appropriate.

Quick HIT

Cardiac Tamponade

Pressures in the RV, LV, RA, LA, pulmonary artery, and pericardium equalize during diastole.

Cardiac Tamponade

A. General Characteristics

1. Defined as accumulation of pericardial fluid. It is the **rate** of fluid accumulation that is important, not the amount.
   a. Two hundred milliliters of fluid that develops rapidly (i.e., blood secondary to trauma) can cause cardiac tamponade.
   b. Two liters of fluid may accumulate slowly before cardiac tamponade occurs. When fluid accumulates slowly, the pericardium has the opportunity to stretch and adapt to the increased volume (i.e., related to a malignancy).
2. Pathophysiology
   a. Pericardial effusion that mechanically impairs diastolic filling of the heart.
   b. Characterized by the elevation and equalization of intracardiac and intrapericardial pressures.
      - Pressures in the RV, LV, RA, LA, pulmonary artery, and pericardium equalize during diastole.
      - Ventricular filling is impaired during diastole.
      - Decreased diastolic filling leads to decreased stroke volume and decreased cardiac output.
3. Causes (see above for pericardial effusion)
   a. Penetrating (less commonly blunt) trauma to the thorax, such as gunshot and stab wounds
   b. Iatrogenic: Central-line placement, pacemaker insertion, pericardiocentesis, etc.
   c. Pericarditis, progressive pericardial effusion
   d. Post-MI with free wall rupture
   e. Aortic dissection

Quick HIT

Beck Triad (Cardiac Tamponade)
- Hypotension
- Muffled heart sounds
- Elevated JVP

B. Clinical Features

1. Cardiac tamponade is a *clinical diagnosis*. Echocardiography can be helpful in confirming tamponade physiology, but the diagnosis can be made without it. The key findings are Beck triad and pulsus paradoxus
2. Beck triad: Hypotension, muffled heart sounds, elevated JVP (distended neck veins, whose venous waveforms show prominent x descent and absent y descent)
3. *Pulsus paradoxus* (tamponade physiology)
   a. Exaggerated decrease in arterial pressure during inspiration (>10 mm Hg drop).
   b. This happens because during inspiration and diastole, blood flows into the RV, and with the effusion compressing the free wall of the RV, it will expand into the interventricular septum and limit the filling of the LV, resulting in diminished stroke volume and therefore blood pressure
   c. Can be detected by a decrease in the amplitude of the femoral or carotid pulse during inspiration
      - Pulse gets strong during expiration and weak during inspiration.
4. *Narrowed* pulse pressure (due to decreased stroke volume).

C. Diagnosis

1. Echocardiogram (Figure 1-14)
   a. Must be performed if suspicion of tamponade exists based on history/examination
   b. Usually diagnostic; the most sensitive and specific noninvasive test for determining tamponade physiology
2. CXR
   a. Enlargement of cardiac silhouette when >250 mL has accumulated
   b. Clear lung fields
3. ECG
   a. *Electrical alternans* (alternate beat variation in the direction of the ECG waveforms)—due to pendular swinging of the heart within the pericardial space, causing a motion artifact
   b. *Findings* are neither 100% sensitive nor specific. ECG should not be used to diagnose tamponade
4. Cardiac catheterization

a. Shows equalization of pressures in all chambers of the heart
b. Shows elevated right atrial pressure with loss of the y descent

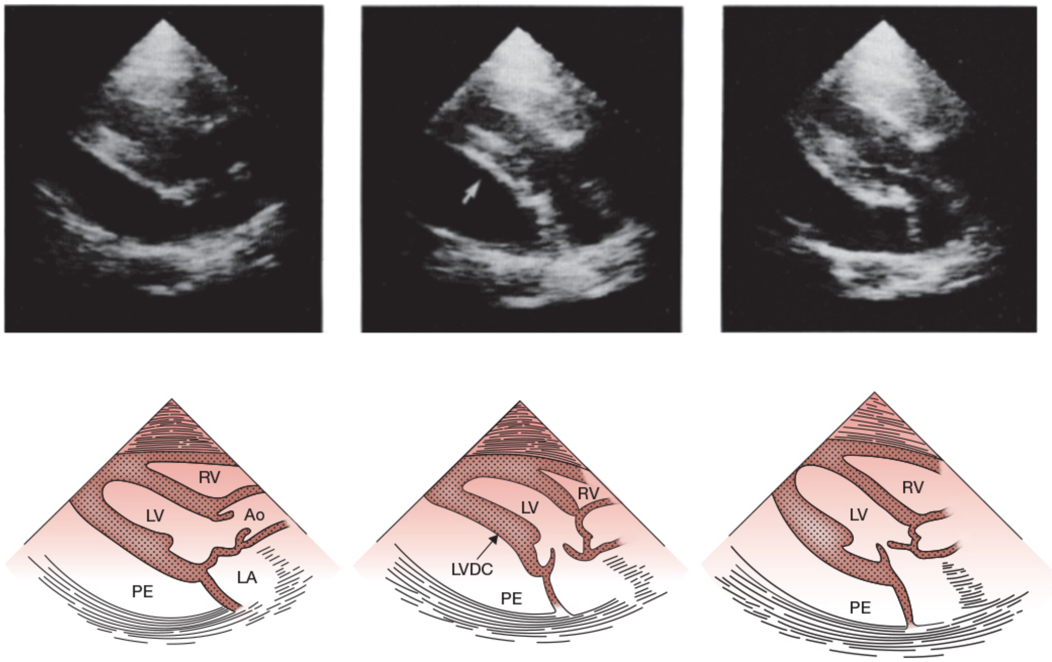


FIGURE 1-14 **Serial echocardiographic images in the parasternal long-axis view from a postoperative patient with cardiac tamponade show a large posterior pericardial effusion (PE). Right ventricle (RV) is adherent to the anterior chest wall. Contour of the left ventricular (LV) free wall is normal at end systole. During early diastole, however, LV posterior wall invaginates inward, which is identified by the *arrow* as LV diastolic collapse (LVDC). This LVDC is only transient; by late diastole, LV has assumed its normal contour. LA, left atrium; Ao, aorta.**
(Reproduced (**top**) and redrawn (**bottom**) with permission from Chuttani K, Pandian NG, Mohanty PK, et al. Left ventricular diastolic collapse: an echocardiographic sign of regional cardiac tamponade. *Circulation* 1991;83(6):1999–2006. Copyright © 1991 by American Heart Association.)

D. Treatment

1. Nonhemorrhagic tamponade
   a. If patient is hemodynamically stable
      - Monitor closely with echocardiogram, CXR, ECG

- If patient has known renal failure, dialysis is more helpful than pericardiocentesis

b. If patient is not hemodynamically stable
- Pericardiocentesis is indicated
- If no improvement is noted, fluid challenge may improve symptoms

2. Hemorrhagic tamponade secondary to trauma
   a. If the bleeding is unlikely to stop on its own, emergent surgery is indicated to repair the injury
   b. Pericardiocentesis is only a temporizing measure and is not definitive treatment. Surgery should **not** be delayed to perform pericardiocentesis

A 57-year-old woman with hypertension and end-stage renal disease presents to the hospital with worsening confusion and hypotension. According to her husband, she has been compliant with her medications and diet. She receives dialysis 2 times weekly, with her last session occurring 4 days ago. On examination, she is hypotensive with distant heart sounds and distended neck veins. An echocardiogram is performed which shows a moderate amount of pericardial fluid with collapse of the right atrium during diastole. A blood pressure cuff is placed on the patient and she is asked to take a deep breath.

Which of the following changes will take place during inspiration? (Note: RV is right ventricle, LV is left ventricle, PVC is pulmonary vascular compliance.)

	Blood Pressure	RV Volume	LV Volume	PVC
A.	Decreased	Increased	Decreased	Increased
B.	Decreased	Decreased	Decreased	Decreased
C.	Decreased	Decreased	Decreased	Increased
D.	Increased	Increased	Decreased	Decreased

- **The answer is A: Decreased blood pressure, increased RV volume, decreased LV volume, increased PVC.** This patient is presenting with Beck's triad of cardiac tamponade: distant heart sounds, elevated jugular venous pressure, and hypotension. Patients with a history of advanced renal disease are at risk for uremic pericarditis, which may or may not present with chest pain. Effusions are typically present and may develop into tamponade. In cardiac tamponade, the surrounding pericardial fluid causes equalization of pressure within the four heart chambers and leads to obstruction of blood flow without pulmonary edema. During inspiration, the negative intrathoracic pressure draws blood into the

right ventricle, increasing the volume of the right ventricle and causing the interventricular septum to shift and decrease the volume of the left ventricle. In addition, pulmonary vascular compliance is increased during inspiration (increased volume of the lung parenchyma and vasculature), which also decreases preload to the left ventricle. This results in a reduced stroke volume of the left ventricle and a decrease in blood pressure. Although a small decrease in systolic blood pressure occurs in healthy patients during inspiration, a decrease ≥10 mmHg is defined as pulsus paradoxus and is commonly seen with cardiac tamponade. Treatment of uremic pericarditis involves increasing the frequency or duration of hemodialysis. Because she is currently having tamponade physiology, she will require pericardiocentesis to remove the pericardial fluid.

Valvular Heart Disease

Mitral Stenosis

A. General Characteristics

1. Almost all cases are due to rheumatic heart disease. (Patient may not recall a history of rheumatic fever.)
2. Pathophysiology
   a. Immune-mediated damage to the mitral valve (due to rheumatic fever) caused by cross-reactivity between the streptococcal antigen and the valve tissue leads to scarring and narrowing of the mitral valve orifice.
   b. Mitral stenosis results in elevated left atrial and pulmonary venous pressure leading to pulmonary congestion.
   c. Anything that increases flow across the mitral valve (exercise, tachycardia, and so on) exacerbates the pulmonary venous HTN and associated symptoms.

d. Long-standing mitral stenosis can result in pulmonary HTN and ultimately can result in right ventricular failure (RVF).
e. Long-standing mitral stenosis can also lead to AFib due to increased left atrial pressure and size.
f. Patients are usually asymptomatic until the mitral valve area is reduced to approximately 1.5 cm^2 (normal valve area is 4 to 5 cm2).

B. Clinical Features

1. Symptoms
   a. Exertional dyspnea, orthopnea, PND
   b. Palpitations, chest pain
   c. Hemoptysis—as the elevated LA pressure ruptures anastomoses of small bronchial veins
   d. Thromboembolism—often associated with AFib
   e. If RV failure occurs, ascites and edema may develop
2. Signs
   a. Mitral stenosis murmur.
      - The *opening snap* is followed by a *low-pitched diastolic rumble* and presystolic accentuation. This murmur increases in length as the disease worsens.
      - Heard best with bell of stethoscope in left lateral decubitus position.
   b. S_2 is followed by an opening snap. The distance between S_2 and the opening snap can give an indication as to the severity of the stenosis. The closer the opening snap follows S_2, the worse is the stenosis.
   c. Murmur is followed by a *loud S*1. A loud S_1 may be the most prominent physical finding.
   d. With long-standing disease, will find signs of RVF (e.g., right ventricular heave, JVD, hepatomegaly, ascites) and/or pulmonary HTN (loud P_2).
   e. All signs and symptoms will increase with exercise and during pregnancy.

C. Diagnosis

1. CXR: Left atrial enlargement (early)
2. Echocardiogram—most important test in confirming diagnosis

a. Left atrial enlargement
b. Thick, calcified mitral valve
c. Narrow, “fish mouth”–shaped orifice

D. Treatment

1. Medical: not curative; pharmacologic management is used as a bridge to surgical treatment or if persistent symptoms despite surgery
   a. Diuretics—for pulmonary congestion and edema
   b. β-Blockers—to decrease heart rate (increase diastolic time to improve LV filling and LA emptying) and cardiac output
   c. Anticoagulation if atrial fibrillation, or history of atrial thrombus or embolic event.
2. Surgical (for severe disease)
   a. Options include percutaneous balloon valvuloplasty and open mitral valve surgery

Quick HIT

Altogether, only one-fourth of patients with *symptomatic* AS survives 3 years in the absence of aortic valve replacement (i.e., the 3-year mortality rate is 75% without surgery).

Aortic Stenosis

A. General Characteristics

1. Pathophysiology
   a. Causes obstruction to LV outflow, which results in LVH.
   b. When the aortic valve area falls below 1 cm^2, cardiac output fails to increase with exertion, causing angina (but may be normal at rest).
   c. With long-standing AS, the LV dilates, causing progressive LV dysfunction.
   d. With severe AS, LV dilation pulls the mitral valve annulus apart, causing MR.
2. Causes
   a. Calcification of a congenitally abnormal bicuspid aortic valve

   b. Calcification of tricuspid aortic valve in elderly
   c. Rheumatic fever
3. Course
   a. Patients are often asymptomatic for years (until middle or old age) despite severe obstruction
   b. Development of angina, syncope, or heart failure is a sign of poor prognosis. Survival is similar to that of the normal population before the development of these three classic symptoms. Without surgical intervention, the survival is poor:
      - Angina (35%)—average survival, 3 years
      - Syncope (15%)—average survival, 2 years
      - Heart failure (50%)—average survival, 1.5 years

B. Clinical Features

1. Symptoms
   a. Angina
   b. Syncope—usually exertional
   c. Heart failure symptoms, such as dyspnea on exertion, orthopnea, or PND
2. Signs
   a. Murmur
      - Harsh crescendo–decrescendo systolic murmur
      - Heard in second right intercostal space
      - Radiates to carotid arteries
   b. *Soft S2.* S2 may also be single since the aortic component may be delayed and merge into P2. The softer the murmur, the more severe the AS
   c. S_4 with progressive disease
   d. *Parvus et tardus*—diminished and delayed carotid upstrokes
   e. Sustained PMI
   f. Precordial thrill

Quick HIT

Management of AS is straightforward:

- If asymptomatic: No treatment
- If symptomatic: Surgical aortic valve replacement or transcatheter aortic valve replacement (TAVR) depending on patient risk

C. Diagnosis

1. CXR findings: Calcific aortic valve, enlarged LV/LA (late)
2. ECG findings: LVH, LA abnormality
3. Echocardiography: Has replaced cardiac catheterization as *standard test* for hemodynamic and valve measurements for diagnosis of AS. Shows thickened, calcified aortic valve leaflets with limited mobility. Key measurements for diagnosis and severity are diminished valve area and increased ventricular-aortic pressure gradient
4. Exercise stress testing is indicated for asymptomatic patients with severe AS to confirm asymptomatic status. These patients, despite having severe AS, do not require intervention. Should *not* be performed in symptomatic patients
5. Cardiac catheterization
   a. Now used primarily in patients in whom echocardiography is nondiagnostic (i.e., poor visualization of valve, difficulty obtaining pressure gradients with Doppler)
   b. Useful in symptomatic patients before surgery because it can also reveal coronary anatomy, allowing the surgeon to do both CABG and aortic valve replacement in patients with both CAD and severe AS

D. Treatment

1. Medical therapy has a limited role.
2. Surgical therapy: *Aortic valve replacement is the treatment of choice.* It is indicated in all symptomatic patients. There is evidence (PARTNER A, PARTNER II trials) that transcatheter aortic valve replacement (TAVR) is noninferior (mortality, stroke risk) to surgical AVR in patients with high and intermediate surgical risk.

Aortic Regurgitation

A. General Characteristics

1. Pathophysiology
   a. Also called aortic insufficiency; this condition is due to inadequate closure of the aortic valve leaflets. Regurgitant blood flow increases left ventricular end-diastolic volume.
   b. LV dilation and hypertrophy occur in response in order to maintain stroke volume and prevent diastolic pressure from increasing excessively.
   c. Over time, these compensatory mechanisms fail, leading to increased left-sided and pulmonary pressures.
   d. The resting left ventricular EF is usually normal until advanced disease.
2. Course
   a. For chronic aortic regurgitation, survival is 75% at 5 years.
      - After the development of angina, death usually occurs within 4 years.
      - After the development of heart failure, death usually occurs within 2 years.
   b. For acute aortic regurgitation, mortality is particularly high without surgical repair.

B. Causes

1. Acute
   a. Infective endocarditis
   b. Trauma
   c. Aortic dissection
   d. Iatrogenic as during a failed replacement surgery
2. Chronic
   a. Primary valvular: Rheumatic fever, bicuspid aortic valve, Marfan syndrome, Ehlers–Danlos syndrome, ankylosing spondylitis, SLE
   b. Aortic root disease: Syphilitic aortitis, osteogenesis imperfecta, aortic dissection, Behçet syndrome, Reiter syndrome, systemic HTN

Quick HIT

Other Physical Findings in Aortic Insufficiency
- De Musset sign: Head bobbing (rhythmical jerking of head)
- Müller sign: Uvula bobs
- Duroziez sign: Pistol-shot sound heard over the femoral arteries

C. Clinical Features

1. Symptoms
   a. Dyspnea on exertion, PND, orthopnea
   b. Palpitations—worse when lying down
   c. Angina
   d. Cyanosis and shock in acute aortic regurgitation (medical emergency)
2. Physical examination
   a. *Widened pulse pressure*—markedly increased systolic BP, with decreased diastolic BP.
   b. Diastolic decrescendo murmur best heard at left sternal border.
   c. *Corrigan pulse* (water-hammer pulse)—rapidly increasing pulse that collapses suddenly as arterial pressure decreases rapidly in late systole and diastole; can be palpated at wrist or femoral arteries.
   d. *Austin Flint murmur*—low-pitched diastolic rumble due to competing flow anterograde from the LA and retrograde from the aorta. It is similar to the murmur appreciated in mitral stenosis.
   e. Displaced PMI (down and to the left) and S_3 may also be present.
   f. Murmur intensity increases with sustained handgrip. Handgrip increases systemic vascular resistance (SVR), which causes an increased “backflow” through the incompetent aortic valve.

D. Diagnosis

1. CXR findings: Enlarged cardiac silhouette, dilated aorta
2. ECG findings: LVH
3. Echocardiogram—Perform serially in chronic, stable patients to assess need for surgery
   a. Assess LV size and function
   b. Look for dilated aortic root and reversal of blood flow in aorta

c. In acute aortic regurgitation, look for early closure of mitral valve

4. Cardiac catheterization: To assess severity of aortic regurgitation and degree of LV dysfunction

E. Treatment

1. If asymptomatic with normal LV function, no therapy indicated.
2. If asymptomatic with severe AR and LV dysfunction, ACEi or ARB indicated for afterload reduction.
3. If symptomatic: Salt restriction, diuretics, afterload reduction (i.e., ACEis or ARBs), HFrEF therapy if heart failure (i.e., β-blocker, aldosterone antagonist, digoxin in selected cases), and restriction on strenuous activity.
4. Definitive treatment is surgery (aortic valve replacement). This should be considered in symptomatic patients, or in those with significant LV dysfunction on echocardiogram.
5. Acute AR (e.g., post-MI): Medical emergency—emergent aortic valve replacement!

Mitral Regurgitation

A. General Characteristics

1. Pathophysiology
   a. Acute
      - Abrupt elevation of left atrial pressure in the setting of normal LA size and compliance, causing backflow into pulmonary circulation with resultant pulmonary edema
      - Cardiac output decreases because of decreased forward flow, so hypotension and shock can occur

   b. Chronic
      - Gradual elevation of left atrial pressure in the setting of dilated LA and LV (with increased left atrial compliance)
      - LV dysfunction occurs due to dilation
      - Pulmonary HTN can result from chronic backflow into pulmonary vasculature
2. Causes

a. Acute
- Endocarditis (most often *Staphylococcus aureus*)
- Papillary muscle rupture (from infarction) or dysfunction (from ischemia)
- Chordae tendineae rupture

b. Chronic
- Mitral valve prolapse (MVP)
- Rheumatic fever
- Marfan syndrome
- Cardiomyopathy causing dilation of mitral annulus

3. Prognosis
   a. Acute form is associated with much higher mortality
   b. Survival is related to extent of LV cavity dilation

B. Clinical Features

1. Symptoms
   a. Dyspnea on exertion, PND, orthopnea
   b. Palpitations
   c. Pulmonary edema
2. Signs
   a. *Holosystolic murmur* (starts with S_1 and continues on through S_2) *at the apex*, which radiates to the back or clavicular area, depending on which leaflet is involved
   b. AFib is a common finding
   c. Other findings: Diminished S_1, widening of S_2, S_3 gallop; laterally displaced PMI; loud, palpable P_2

C. Diagnosis

1. CXR findings: Cardiomegaly, dilated LV, pulmonary edema.
2. Echocardiogram: MR; dilated LA and LV; decreased LV function. Should be performed serially in patients with known MR.

D. Treatment

1. Medical

a. Afterload reduction with vasodilators is recommended for symptomatic patients only; they are not recommended in most asymptomatic patients as they may mask progression of the disease
b. Chronic anticoagulation if patient has AFib
c. IABP can be used as a bridge to surgery for acute MR (decreases afterload and favors normal flow, not regurgitant flow)

2. Surgical
   a. Mitral valve repair or replacement
   b. Must be performed before left ventricular function is too severely compromised
   c. Patients with very high surgical risk, severe symptoms, and favorable anatomy may be candidates for transcatheter mitral valve repair

Tricuspid Regurgitation

A. General Characteristics

1. Tricuspid regurgitation (TR) results from a failure of the tricuspid valve to close completely during systole, causing regurgitation of blood into the RA. It is estimated that up to 70% of normal adults have mild, physiologic TR as seen on high-resolution echocardiography. A much smaller percentage of people are actually symptomatic.
2. Causes—up to 90% of cases occur in people with anatomically normal valve leaflets and chords.
   a. TR is usually secondary to RV dilation. Any cause of RV dilation can result in enlargement of the tricuspid orifice.
      - Left ventricular failure is the most common cause.
      - Right ventricular infarction.
      - Inferior wall MI.
      - Cor pulmonale, secondary to pulmonary HTN.
   b. Tricuspid endocarditis—seen in *IV drug users*.
   c. May be secondary to rheumatic heart disease; usually accompanied by mitral and aortic valve disease.
   d. Ebstein anomaly—congenital malformation of tricuspid valve in which there is downward displacement of the valve into the RV.

e. Other causes include carcinoid syndrome, SLE, and myxomatous valve degeneration.

B. Clinical Features

1. Usually asymptomatic unless the patient develops symptoms of RHF/pulmonary HTN
2. Signs and symptoms of RVF (ascites, hepatomegaly, edema, JVD)
3. Pulsatile liver
4. Prominent V waves in jugular venous pulse with rapid y descent
5. Inspiratory S_3 along LLSB may be present
6. Blowing holosystolic murmur
   a. At LLSB
   b. Intensified with inspiration; reduced during expiration or the Valsalva maneuver
7. Right ventricular pulsation along LLSB
8. AFib can be present with severe atrial dilation

C. Diagnosis

1. Echocardiogram
   a. Quantifies amount of TR
   b. Identifies prolapse/flail of tricuspid valve leaflets
   c. Estimates pulmonary pressures based on severity of TR velocity
   d. ECG: RV and RA enlargement

D. Treatment

1. Treat any underlying etiology of symptomatic TR
2. Diuretics for volume overload and venous congestion/edema
3. Treat left-sided heart failure, endocarditis, or pulmonary HTN
4. Severe regurgitation may be surgically corrected if pulmonary HTN is not present
   a. Native valve repair surgery
   b. Valvuloplasty of tricuspid ring
   c. Valve replacement surgery: Rarely performed

Mitral Valve Prolapse

A. General Characteristics

1. MVP is defined as the presence of excessive or redundant mitral leaflet tissue due to myxomatous degeneration of mitral valve leaflets and/or chordae tendineae. The redundant leaflet(s) prolapse toward the LA in systole, which results in the auscultated click and murmur.
2. MVP is common in patients with genetic connective tissue disorders, such as Marfan syndrome, osteogenesis imperfecta, and Ehlers–Danlos syndrome.
3. MVP is a common cause of MR in developed countries.
4. Arrhythmias and sudden death are very rare.

Quick HIT

Key Signs of MVP

- Systolic clicks
- Midsystolic rumbling murmur that increases with standing and the Valsalva maneuver and decreases with squatting

B. Clinical Features

1. Symptoms
   a. Most patients are asymptomatic for their entire lives.
   b. Palpitations and atypical chest pain may occur.
   c. *TIAs* due to emboli from mitral valve have been reported, but are very rare.
2. Signs
   a. Midsystolic or late systolic click(s).
   b. Mid-to-late systolic murmur.
   c. Some patients have midsystolic click without the murmur; others may have the murmur without the click.
   d. Standing and the Valsalva maneuver *increase* murmur and click because these maneuvers reduce LV chamber size, allowing the click and murmur to occur earlier in systole.
   e. Squatting *decreases* murmur and click because it increases LV chamber size, thus delaying the onset of the click and murmur.

C. Diagnosis

1. Echocardiogram is the most useful.
2. Most patients are asymptomatic, so diagnosis is typically made on the basis of the murmur and echocardiogram alone.

D. Treatment

1. If patient is asymptomatic, reassurance. There is some association between MVP and anxiety, so all patients should be reassured about the benign nature of this condition.
2. For chest pain, β-blockers have been useful, but they are unlikely to be required.
3. Surgery is rarely required. The condition is generally benign.

Rheumatic Heart Disease

A. General Characteristics

1. Rheumatic heart disease occurs as a complication of streptococcal pharyngitis (group A streptococcus).
2. Acute rheumatic fever is an immunologically mediated systemic process that may progress to rheumatic heart disease.
3. Rheumatic heart disease describes the chronic valvular abnormalities secondary to acute rheumatic fever.
4. The most common valvular abnormality is mitral stenosis, but patients may have aortic or tricuspid involvement as well.
5. The incidence of rheumatic heart disease has fallen drastically in industrialized countries and with widespread antibiotic usage, but remains a significant cause of morbidity and mortality in developing countries.

B. Diagnosis of Acute Rheumatic Fever Based on the Revised Jones Criteria (requires two major criteria or one major and two minor criteria)

1. Major criteria
   a. Migratory polyarthritis
   b. Erythema marginatum

c. Cardiac involvement (e.g., pericarditis, CHF, valve disease)
d. Chorea
e. Subcutaneous nodules

2. Minor criteria
a. Fever
b. Elevated erythrocyte sedimentation rate
c. Polyarthralgias
d. Prior history of rheumatic fever
e. Prolonged PR interval
f. Evidence of preceding streptococcal infection

C. Treatment

1. Treat streptococcal pharyngitis with a penicillin (penicillin or amoxicillin), cephalosporin, or macrolide (azithromycin or clarithromycin) antibiotic if penicillin allergy to prevent rheumatic fever.
2. Acute rheumatic fever is treated with NSAIDs. C-reactive protein is used to monitor treatment.
3. Treat the valvular pathology of rheumatic heart disease.

Quick HIT

Always suspect endocarditis in a patient with a new heart murmur and unexplained fever or bacteremia.

Infective Endocarditis

A. General Characteristics

1. Infective endocarditis is defined as an infection of the endocardial surface of the heart (usually involves the cusps of the valves)
2. Classifications (can be classified as acute or subacute)
a. Acute endocarditis
1. Most commonly caused by *S. aureus* (highly virulent)
2. Occurs on a normal heart valve
3. If untreated, fatal in less than 6 weeks

b. Subacute endocarditis
   - Caused by less virulent organisms, such as *Streptococcus viridans* and *Enterococcus*
   - Occurs on damaged heart valves
   - If untreated, takes much longer than 6 weeks to cause death

c. Can also be classified as right-sided or left-sided, and whether it affects a native valve or a prosthetic valve

3. Organisms

a. Native valve endocarditis
   - Common organisms include *Staphylococcus* species (*S. aureus* more commonly than *Staphylococcus epidermidis*), Viridans group streptococci, and *Enterococci.*
   - *Streptococcus bovis* is associated with increased risk of active colonic malignancy
   - **HACEK** group of organisms: *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*

b. Prosthetic valve endocarditis
   - Staphylococci are the most common causes of early-onset endocarditis; symptoms appear within 60 days of surgery (*S. epidermidis* more commonly than *S. aureus*).
   - Streptococci are the most common cause of late-onset endocarditis; symptoms appear 60 days after surgery.

c. Endocarditis in persons who inject drugs
   - Frequently presents with right-sided endocarditis.
   - *S. aureus* is the most common cause.
   - Other organisms include *Enterococci* and *Streptococci.* Fungi (mostly *Candida*) and gram-negative rods (mostly *Pseudomonas*) are less common causes.

4. Complications

a. Heart failure due to valvular damage

b. Paravalvular abscess (can result in conduction abnormalities such as AV block)

c. Various solid organ damage from showered emboli: Septic pulmonary emboli, intramuscular abscesses, Roth spots (retinal), Janeway lesions (microabscesses in extremities), septic arthritis,

epidural spinal abscess, renal abscesses, cerebral emboli causing CVA or brain abscess

d. Glomerulonephritis
e. Osler nodes (immunologic depositions in extremities, painful), splinter hemorrhages in nail beds

Quick HIT

TEE is better than transthoracic echocardiography (TTE) in the diagnosis of endocarditis for especially mitral valve pathology and small aortic vegetations. Most patients should get TTE as an initial screening test.

Quick HIT

Infective endocarditis is almost always fatal if left untreated.

B. Diagnosis

1. Modified Duke criteria (Table 1-3): Two major criteria, one major and three minor criteria, or five minor criteria are required to diagnose "definite infective endocarditis." "Possible infective endocarditis" consists of one major and one minor, or three minor criteria.
2. Of note, echocardiographic evidence of vegetations is not necessary to make the diagnosis as long as sufficient Duke criteria have been met. Treatment should be initiated if clinical suspicion is high.

TABLE 1-3 Duke Criteria

Major	Minor
• **Sustained bacteremia** by an organism known to cause endocarditis • **Endocardial involvement** documented by either echocardiogram (vegetation, abscess, valve perforation, prosthetic dehiscence) or clearly established **new valvular regurgitation**	• **Predisposing condition** (abnormal valve or abnormal risk of bacteremia) • **Fever** • **Vascular phenomena:** Septic arterial or pulmonary emboli, mycotic aneurysms, intracranial hemorrhage, Janeway lesions[a] • **Immune phenomena:** Glomerulonephritis, Osler nodes,[b] Roth spots,[c] rheumatoid factor • **Positive blood cultures** not meeting major criteria • **Positive echocardiogram** not meeting major criteria

Note: Definitive (i.e., highly probable) diagnosis if two major, or one major plus three minor, or five minor criteria are present.

[a]Janeway lesions are painless erythematous lesions on palms and soles.

[b]Osler nodes are painful, raised lesions of fingers, toes, or feet.

[c]Roth spots are oval, retinal hemorrhages with a clear, pale center.

Reprinted from Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med* 1994;96(3):200–209. Copyright © 1994 Elsevier. With permission.

Quick HIT

The diagnosis of infective endocarditis is made with the modified Duke criteria. A negative echocardiogram does not rule out endocarditis if other criteria are met.

C. Treatment

1. Three sets of blood cultures should be drawn prior to initiating antibiotic therapy
2. Empiric antibiotic therapy should include coverage of staphylococci, streptococci, and enterococci
3. Parenteral antibiotics based on culture results for extended periods (up to 6 weeks)

4. If patient has intracardiac devices such as pacemaker or ICD, these must be *removed*
5. Early surgical intervention is warranted for patients with:
   - Acute heart failure due to valvular damage
   - Left-sided infective endocarditis with highly resistant organisms (including MRSA)
   - Infective endocarditis complicated by heart block or intracardiac abscess
   - Persistent bacteremia or fevers lasting 5 to 7 days after antibiotic initiation
   - Recurrent infection in those with prosthetic valves

D. Prophylaxis

Scope of patients who qualify for prophylaxis is much narrower than in the past. Must have both a qualifying cardiac indication **AND** procedure to warrant antibiotic prophylaxis.

1. Qualifying cardiac indications
   a. Prosthetic heart valves (including mechanical, bioprosthetic, and transcatheter valves)
   b. History of infective endocarditis
   c. Congenital heart disease
      - Unrepaired cyanotic congenital heart disease
      - Repaired congenital heart disease, with prosthetic material, during first 6 months after procedure
   d. Cardiac transplant with valvulopathy
2. Qualifying procedures
   a. Dental procedures involving manipulation of gingival mucosa or periapical region of teeth (extractions, implants, periodontal surgery, cleaning when bleeding expected)
   b. Procedures involving biopsy or incision of respiratory mucosa
   c. Procedures involving infected skin or musculoskeletal tissue

Quick HIT

Do NOT give antibiotics for endocarditis prophylaxis for:
- Native mitral valve prolapse/stenosis
- Routine GI (endoscopy) or GU (cystoscopy) procedures

Nonbacterial Thrombotic Endocarditis (Marantic Endocarditis)

- Associated with debilitating illnesses such as metastatic cancer (found in up to 20% of cancer patients).
- Sterile deposits of fibrin and platelets form along the closure line of cardiac valve leaflets.
- Vegetations can embolize to the brain or periphery.
- Although the use of heparin may be appropriate, no studies have confirmed its efficacy.

Nonbacterial Verrucous Endocarditis (Libman–Sacks Endocarditis)

- Typically involves the aortic valves in individuals with SLE
- Characterized by the formation of small warty vegetations on **both sides** of valve leaflets and may present with regurgitant murmurs
- Rarely gives rise to infective endocarditis, but can be a source of systematic embolization
- Treat underlying SLE and anticoagulate

Quick HIT

Congenital heart disease accounts for only 2% of heart disease in adults.

Congenital Heart Diseases

Atrial Septal Defect

A. General Characteristics (Types)

1. Ostium secundum (most common—80% of cases)—occurs in central portion of interatrial septum
2. Ostium primum—occurs low in the septum
3. Sinus venosus defects—occurs high in the septum

B. Pathophysiology

1. Oxygenated blood from the LA passes into the RA, increasing right heart output and thus pulmonary blood flow.
2. Leads to increased work of the right side of the heart: As shunt size increases, RA and RV dilation occurs with pulmonary-to-systemic flow ratios greater than 1.5:1.0.
3. Pulmonary HTN is a serious sequela, but is rare in ASD.

C. Clinical Course

1. Patients are usually asymptomatic until middle age (around 40).
2. Thereafter, symptoms may begin and include exercise intolerance, dyspnea on exertion, and fatigue.
3. If mild, patients can live a normal lifespan.

D. Clinical Features

1. Mild systolic ejection murmur at pulmonary area secondary to increased pulmonary blood flow
2. Fixed split S_2
3. Diastolic flow “rumble” murmur across tricuspid valve area secondary to increased blood flow
4. In advanced disease, signs of RV failure may be seen

E. Diagnosis

1. TEE is diagnostic (better than TTE). Contrast echocardiography can improve resolution. A so-called "bubble study" is a type of contrast echo which involves injecting microbubbles and watching them cross the defect via a right-to-left shunt. This is often used to aid in diagnosis of ASDs.
2. CXR: Large pulmonary arteries; increased pulmonary markings.
3. ECG: Right bundle branch block and right-axis deviation; atrial abnormalities can also be seen (e.g., fibrillation, flutter).

F. Complications

1. Pulmonary HTN—does not occur before 20 years of age, but is a common finding in patients over 40
2. **Eisenmenger disease** is a late complication seen in a minority of patients, in which irreversible pulmonary HTN leads to reversal of shunt, heart failure, and cyanosis
3. Right heart failure
4. Atrial arrhythmias, especially AFib
5. Stroke can result from paradoxical emboli or AFib

G. Treatment

1. Unless they are very large, most defects do not require closure.
2. Surgical repair when pulmonary-to-systemic blood flow ratio is greater than 1.5:1.0 or 2:1 or if patient is symptomatic.

Ventricular Septal Defect

A. General Characteristics

1. Ventricular septal defect is the most common congenital cardiac malformation
2. Pathophysiology
   a. Blood flows from the LV (high pressure) into the RV (low pressure) through a hole, resulting in increased pulmonary blood flow. As long as the pulmonary vascular resistance (PVR) is lower than the SVR,

the shunt is left to right. If the PVR increases above the SVR, the shunt reverses.
b. Large defects eventually lead to pulmonary HTN, whereas small defects do not change pulmonary vascular hemodynamics.

B. Clinical Features

1. Symptoms
   a. A small shunt produces no symptoms. Many of these close spontaneously.
   b. A large shunt without elevated PVR (and thus left-to-right shunt) gives rise to CHF, growth failure, and recurrent lower respiratory infections.
   c. A large shunt with very high PVR (Eisenmenger reaction) gives rise to SOB, dyspnea on exertion, chest pain, syncope, and cyanosis.
2. Signs
   a. Harsh, blowing holosystolic murmur with thrill
      - At fourth left intercostal space
      - Murmur increases with handgrip maneuver and decreases with standing
      - The smaller the defect, the louder the holosystolic murmur
   b. Sternal lift (RV enlargement, RV heave)
   c. As PVR increases, the pulmonary component of S_2 increases in intensity
   d. Aortic regurgitation may be seen in some patients

C. Diagnosis

1. ECG: Biventricular hypertrophy predominates when PVR is high.
2. CXR
   a. Enlargement of the pulmonary artery.
   b. Enlargement of cardiac silhouette: As PVR increases (and left-to-right shunt decreases), heart size decreases, but pulmonary artery size increases.
3. Echocardiogram shows the septal defect.

D. Complications

1. Endocarditis

2. Progressive aortic regurgitation
3. Heart failure
4. Pulmonary HTN and shunt reversal (Eisenmenger)

E. Treatment

1. Endocarditis prophylaxis is important but is NOT currently recommended for patients with uncomplicated VSD and no history of endocarditis.
2. Surgical repair is indicated if the pulmonary flow to systemic flow ratio is greater than 1.5:1.0 or 2:1, as well as for patients with infective endocarditis.
3. For the asymptomatic patient with a small defect, surgery is not indicated.

Quick HIT

In women, coarctation of the aorta may be associated with Turner syndrome.

Coarctation of the Aorta

A. General Characteristics

1. Narrowing/constriction of aorta, usually at origin of left subclavian artery near ligamentum arteriosum, which leads to obstruction between the proximal and distal aorta, and thus to increased left ventricular afterload.

B. Clinical Features

1. HTN in upper extremities with hypotension in lower extremities
2. Well-developed upper body with underdeveloped lower half
3. Midsystolic murmur heard best over the back
4. Symptoms include headache, cold extremities, claudication with exercise, and leg fatigue
5. Delayed femoral pulses when compared to radial pulses
6. Prevalence of coarctation of the aorta is increased in patients with Turner syndrome

C. Diagnosis

1. CT angiogram of the chest is diagnostic
2. ECG shows LVH
3. CXR
   a. Notching of the ribs
   b. "Figure 3" appearance due to indentation of the aorta at the site of coarctation, with dilation before and after the stenosis

D. Complications

1. Severe HTN
2. Rupture of cerebral aneurysms
3. Infective endocarditis
4. Aortic dissection

E. Treatment

1. Standard treatment involves surgical decompression.
2. Percutaneous balloon aortoplasty or stenting is also an option in selected cases.

Quick HIT

The leading causes of death in adults with PDA are heart failure and infective endocarditis.

Patent Ductus Arteriosus

A. General Characteristics

1. Communication between aorta and pulmonary artery that persists after birth.
2. During fetal life, prostaglandins and low oxygen tension maintain the ductus arteriosus. Blood is shunted away from nonfunctioning lungs; normally closes within days after birth.
3. Becomes a left-to-right shunt in life outside the womb if it remains patent (blood flows from aorta into pulmonary artery).

4. Associated with congenital rubella syndrome, high altitude, and premature births.
5. Pathophysiology
   a. Large left-to-right shunting results in volume overload, pulmonary HTN, and right-sided heart failure.
   b. Cyanosis occurs late.
   c. May eventually see reversal of blood flow.

Quick HIT

Adults with PDA usually have normal pulmonary pressures.

B. Clinical Features

1. May be asymptomatic
2. Signs of heart failure
3. Loud P_2 (sign of pulmonary HTN)
4. LVH: Secondary to left-to-right shunt
5. Right ventricular hypertrophy: Secondary to pulmonary HTN
6. Continuous "machinery murmur" at left second intercostal space (both systolic and diastolic components)
7. Wide pulse pressure and bounding peripheral pulses
8. Lower extremity clubbing: Toes more likely than fingers to be cyanotic (differential cyanosis)

C. Diagnosis

1. CXR
   a. Increased pulmonary vascular markings
   b. Dilated pulmonary artery
   c. Enlarged cardiac silhouette
   d. Sometimes calcifications of ductus arteriosus
2. Echocardiography reveals the patent ductus and/or turbulent blood flow

D. Treatment

1. If pulmonary vascular disease is absent: Surgical ligation.

2. If severe pulmonary HTN or right-to-left shunt is present, do *not* correct patent ductus arteriosus (PDA). Surgery is contraindicated.
3. Indomethacin indicated for closure. Prostaglandin E_1 can be used to keep the PDA open (may be needed in the face of other cardiac abnormalities such as transposition of the great vessels).

Tetralogy of Fallot

A. General Characteristics

1. Characterized by four cardiac abnormalities: Ventricular septal defect, right ventricular hypertrophy, pulmonary artery stenosis or atresia, and overriding aorta.
2. The exact embryologic variant is unknown, but the four abnormalities likely arise secondary to defects in the development of the infundibular septum.
3. Tetralogy of Fallot (TOF) typically occurs sporadically, but may also be part of a syndrome.

B. Clinical Features

1. Cyanosis is the most common symptom.
2. Degree of clinical symptoms depends largely on the degree of right ventricular outflow obstruction.
3. Patients experience Tet spells—they will squat after exertion such as exercise or crying spell in an infant. This maneuver increases SVR, which helps shunt blood from the RV to the lungs instead of the aorta. Oxygen, morphine, and β-blockers may also be needed if the patient continues to be cyanotic.
4. Murmur is typically crescendo–decrescendo in nature and heard best at the left upper sternal border.

C. Diagnosis

1. Echocardiography is the diagnostic modality of choice. This test can clearly define the four abnormalities as well as provide important information about aortic arch anatomy.
2. EKG may show enlarged RA and RV.
3. CXR classically shows *boot-shaped heart.*

4. Cardiac catheterization may be required in some patients to fully define the anatomy.

D. Treatment

1. Treatment is surgical. Most patients have surgery within the first year of life. Twenty-year survival rates after surgery are above 80%. The most common causes of death are sudden cardiac death and heart failure.
2. Complications after surgery include arrhythmias, pulmonary regurgitation, residual outflow obstruction, and heart failure.

Diseases of the Vasculature

Hypertensive Emergency

A. General Characteristics

1. Hypertensive emergency: Systolic BP ≥180 and/or diastolic BP ≥120 **in addition to end-organ damage—immediate treatment is indicated** (see Clinical Pearl 1-10).

CLINICAL PEARL 1-10

If a patient presents with severe headache and markedly elevated BP:

- The first step is to lower the BP with an antihypertensive agent.
- The second step is to order a CT scan of the head to rule out intracranial bleeding (subarachnoid hemorrhage is in the differential diagnosis for severe headache).
- If the CT scan is negative, one may proceed to a lumbar puncture.

2. Elevated BP levels alone without end-organ damage—referred to as severe asymptomatic HTN (or *hypertensive urgency*). Rarely require emergency therapy and can be managed with attempts to lower BP over a period of 24 hours.

3. Whenever a patient presents with markedly elevated BP, it is critical to assess the following systems for end-organ damage
   a. Eyes: Papilledema
   b. CNS
      - Altered mental status or intracranial hemorrhage
      - Hypertensive encephalopathy may develop (suspect when BP is markedly elevated: 240/140 or higher, along with neurologic findings such as confusion)
   c. Kidneys: Renal failure or oliguria
   d. Heart: UA, MI, HF with pulmonary edema, aortic dissection
   e. Lungs: Pulmonary edema
4. Hypertensive emergency may lead to posterior reversible encephalopathy syndrome (PRES)—a radiographic condition which is postulated to be caused by autoregulatory failure of cerebral vessels as well as endothelial dysfunction.
   a. Despite the name, the syndrome may not always be reversible and can affect regions other than the posterior region of the brain.
   b. Symptoms include insidious onset of headache, altered level of consciousness, visual changes, and seizures. The classic radiographic finding is posterior cerebral white matter edema.
   c. Most patients are hypertensive, but may be normotensive. Elevated blood pressures overwhelm the autoregulatory mechanisms of the cerebral vessels, leading to arteriolar dilation and extravasation of fluid into the brain.
   d. Diagnose with clinical findings and brain MRI. First treatment step is to lower BP, usually with IV medications. Other treatment steps include correcting electrolyte abnormalities and stopping seizures if they occur.

B. Causes

1. Nonadherence with antihypertensive therapy
2. Cushing syndrome
3. Stimulant drugs such as cocaine, LSD, amphetamines
4. Hyperaldosteronism
5. Eclampsia
6. Vasculitis

7. Alcohol withdrawal
8. Pheochromocytoma
9. Nonadherence with dialysis
10. Renal artery stenosis (atherosclerosis or fibromuscular dysplasia)
11. Polycystic kidney disease

C. Treatment

1. Hypertensive emergencies
   a. Reduce mean arterial pressure by 10% to 20% in the first hour, then gradually by another 10% over the remaining 23 hours. The goal is not to immediately achieve normal BP, but to get the patient out of danger, then reduce BP gradually to allow cerebral autoregulation to maintain cerebral perfusion with changing systemic blood pressures.
   b. Always consider other conditions that might affect the rate of correction (e.g., aortic dissections require more rapid BP correction, whereas acute strokes have higher target blood pressures).
   c. If severe (diastolic pressure >130) or if hypertensive encephalopathy is present, **IV agents,** such as esmolol, nitroprusside, labetalol, or nitroglycerin, are appropriate. Hydralazine can be given as an IV push as well.
2. Hypertensive urgencies: BP should be lowered within 24 hours using **oral agents.** Typically does not require hospital admission.

Quick HIT

Hypertensive emergency—evidence of end-organ damage; use IV medications
Hypertensive urgency—no evidence of end-organ damage; use PO medications

Quick HIT

Aortic Dissection

- Type A = ascending; treatment is surgical
- Type B = descending; treatment is medical

Aortic Dissection

A. General Characteristics

1. Predisposing factors
   a. Long-standing systemic HTN (present in 70% of patients)
   b. Cocaine use (may be remote)
   c. Trauma
   d. Connective tissue diseases, such as Marfan syndrome and Ehlers–Danlos syndrome
   e. Bicuspid aortic valve
   f. Coarctation of the aorta
   g. Third trimester of pregnancy
   h. Pre-existing aortic aneurysm
   i. Intimal ulcer due to atherosclerosis
2. Stanford classification (Figure 1-15)
   a. *Type A (proximal)* involves the ascending aorta (includes retrograde extension from descending aorta).
   b. *Type B (distal)* is limited to the descending aorta (distal to the take-off of the subclavian artery).

B. Clinical Features

1. Severe, tearing/ripping/stabbing pain, typically abrupt in onset, either in the anterior or back of the chest (often the interscapular region)
   a. Anterior chest pain is more common with proximal dissection (type A)
   b. Interscapular back pain is more common with distal dissection (type B)
2. Diaphoresis
3. Most are hypertensive, but some may be hypotensive
4. Pulse or BP asymmetry between limbs
5. Aortic regurgitation (especially proximal dissections)
6. Neurologic manifestations (hemiplegia, hemianesthesia) due to obstruction of carotid artery
7. Type A dissection can progress to coronaries (causing MI) or pericardium (causing cardiac tamponade)

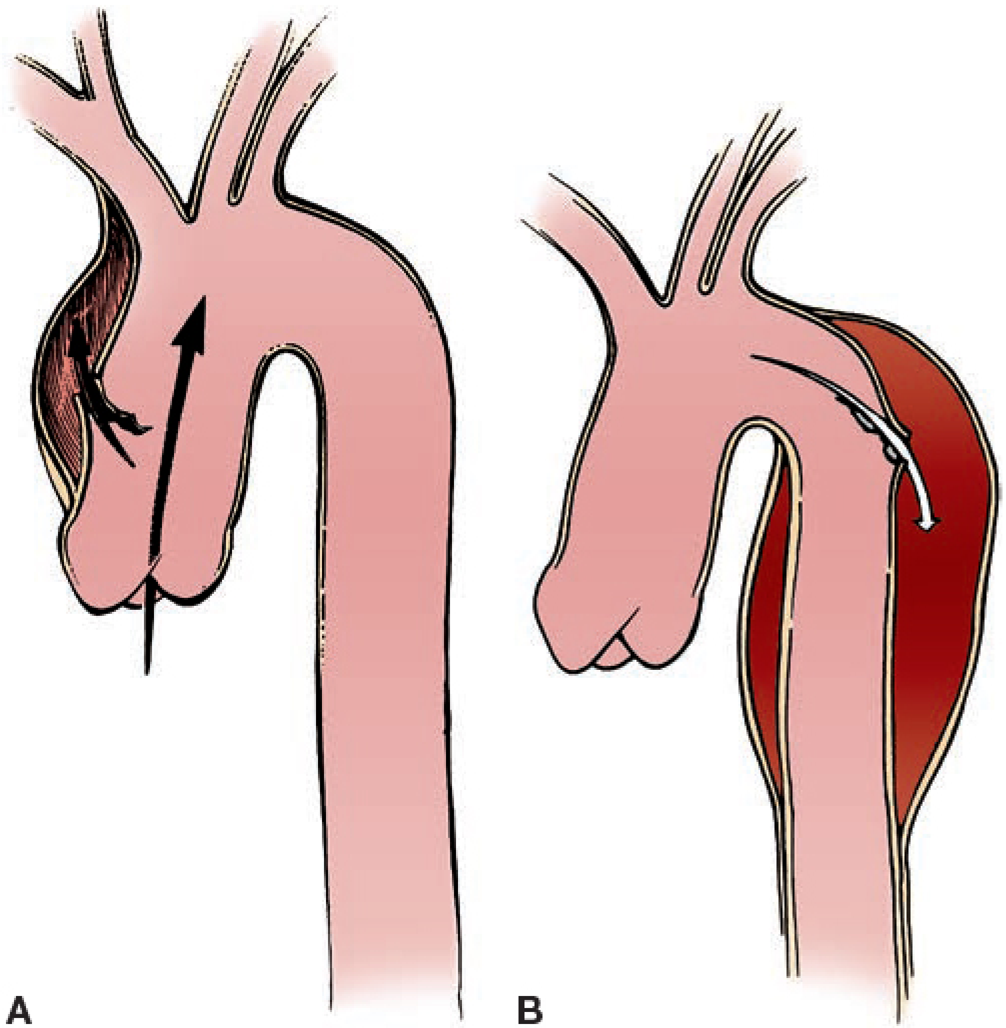


FIGURE 1-15 **Aortic dissection. A: Dissection of ascending aorta. B: Dissection of descending aorta.**
(Modified with permission from Harwood-Nuss A, Wolfson AB, Linden CH, et al. *The Clinical Practice of Emergency Medicine*. 3rd ed. Lippincott Williams & Wilkins; 2000:212. Figure 51.1.)

Quick HIT

The diagnosis of aortic dissection can be difficult to make because the classic clinical findings often are not apparent. The use of thrombolytic therapy in patients with aortic dissection who have been incorrectly diagnosed as having an acute MI can have fatal consequences.

C. Diagnosis

1. CXR shows **widened mediastinum** (>8 mm on AP view).
2. CT angiogram (CTA) and MRI are both highly accurate; MRI takes longer to perform, making it less ideal in the acute setting. The false lumen of the dissection plane appears larger on CT and MRI.
3. TEE has a very high sensitivity and specificity; it is noninvasive and can be performed at the bedside.
4. Aortic angiography was once the gold standard, and has largely been replaced by CTA. It can be used for patients in whom noninvasive imaging is nondiagnostic, or during endovascular intervention for dissection.

Quick HIT

CTA and TEE are the preferred tests in the diagnosis of acute aortic dissection. CTA is much more readily available in emergency rooms. TEE is very accurate and is ideal in the unstable patient because it can be performed at the bedside.

D. Treatment

1. Initiate medical therapy **immediately**
   a. IV β-blockers (labetalol, esmolol) to diminish the force of left ventricular ejection, thus reducing shear stress on intima
   b. Goal systolic BP < 120 mm Hg and HR <60. Start with a β-blocker such as esmolol, then add another IV agent if the SBP is not at goal (e.g., nitroprusside).
2. For type A dissections—surgical management
   a. Most cases of type A dissections should be treated as surgical emergencies to prevent complications such as MI, aortic regurgitation, or cardiac tamponade
   b. Open surgery is still the standard of care
   c. *High* risk of mortality, 1% to 2% per hour after symptom onset without intervention
3. For type B dissections—medical management
   a. Lower blood pressure and heart rate as above
   b. Pain control with morphine or hydromorphone

c. Unrelenting symptoms may require surgical treatment—both open and endovascular surgical options exist

Abdominal Aortic Aneurysm

A. General Characteristics

1. Abdominal aortic aneurysm (AAA) is an abnormal localized dilation of the aorta. Most AAAs occur between the renal arteries and iliac bifurcation.
2. The incidence increases with age. AAAs are rare before the age of 50 years. The average age at time of diagnosis is 65 to 70 years.
3. AAAs are much more common in men, though more likely to rupture in women at a given size.

B. Causes

1. Multifactorial—in most cases, there is atherosclerotic weakening of the aortic wall.
2. Other predisposing factors include trauma, HTN, vasculitis, smoking, and positive family history.
3. Syphilis and connective tissue abnormalities (e.g., Marfan disease) are associated with thoracic aneurysms, but they may involve the lower aorta as well.

C. Clinical Features

1. Usually asymptomatic and discovered on either abdominal examination or a radiologic study done for another reason
2. Sense of “fullness”
3. Pain may or may not be present—if present, located in the hypogastrium and lower back and usually throbbing in character
4. Pulsatile mass on abdominal examination
5. Symptoms suggesting expansion and impending rupture include the following:
   a. Sudden onset of severe pain in the back or lower abdomen, radiating to the groin, buttocks, or legs
   b. *Grey Turner sign* (ecchymoses on back and flanks) and *Cullen sign* (ecchymoses around umbilicus) are signs of retroperitoneal bleeding.

Neither is very sensitive for ruptured AAA

6. Rupture of an AAA
   a. The triad of abdominal pain, hypotension, and a palpable pulsatile abdominal mass indicates a ruptured AAA and emergent laparotomy is indicated. No further diagnostic testing is needed with this constellation of symptoms; however, patients may present with only one or two components of this triad
   b. Cardiovascular collapse
   c. Syncope or near-syncope, secondary to sudden hemorrhage
   d. Nausea and vomiting

D. Diagnosis

1. Ultrasound
   a. Test of choice to evaluate both the location and size of the aneurysm
   b. 100% sensitive in detecting AAAs
2. CT scan
   a. 100% sensitive in detecting AAAs
   b. Takes longer to perform than plain radiographs or ultrasound; should only be used in hemodynamically stable patients
   c. CT is the scan of choice for preoperative planning

Quick HIT

Leriche syndrome: Atheromatous occlusion of distal aorta just above bifurcation causing bilateral claudication, impotence, and absent/diminished femoral pulses.

E. Treatment

1. Unruptured aneurysms
   a. Management largely depends on size of the aneurysm.
      - Data from the ADAM trial and UK-SAT have shown that if the aneurysm is >5 cm in diameter or symptomatic, surgical resection with synthetic graft placement is recommended. (The infrarenal aorta is replaced with a fabric tube.) This can often be done endovascularly by accessing the femoral artery. The diameter of the normal adult infrarenal aorta is about 2 cm.

- The management of asymptomatic aneurysms <5 cm is controversial. Periodic imaging is recommended to follow up growth. Growth of more than 1 cm in a year suggests elevated risk. No “safe” size exists however, and small AAAs **can** rupture.

b. Other factors to consider are the patient’s life expectancy (patient may be more likely to die of other medical illnesses), and the risk of surgery.

2. Ruptured AAAs: Emergency surgical repair is indicated. All of these patients are unstable.
   a. While open repair remains the gold standard, some ruptured AAAs may be repaired endovascularly as well with stents.

Peripheral Arterial Disease

A. General Characteristics

1. Peripheral arterial disease (PAD) is an occlusive atherosclerotic disease of the lower extremities (see also Clinical Pearl 1-11)
2. Patients with PAD usually have coexisting CAD (with CHF, history of MI, and so on) and other chronic medical problems (e.g., diabetes, lung disease)
3. Sites of occlusion/stenosis
   a. Superficial femoral artery (in Hunter canal) is the most common site
   b. Popliteal artery
   c. Aortoiliac occlusive disease
4. Risk factors
   a. Smoking is by far the most important risk factor
   b. CAD, hyperlipidemia, HTN
   c. Diabetes—prevalence is markedly increased in these patients
5. Prognosis
   a. If the patient has intermittent claudication, the prognosis is generally good
   b. Patients with rest pain or ischemic ulcers have the worst prognosis (especially in diabetics or smokers)

CLINICAL PEARL 1-11

Evaluation of a Patient With PAD

- Evaluate the cardiovascular system (HTN, carotid bruits, murmurs, AAA).
- Assess arterial pulses.
- Inspect lower extremities for color change, ulcers, muscle atrophy, hair loss, thickened toenails, etc.
- Consider the following tests: ECG, CBC, renal function tests, and coagulation profile (factor V Leiden, antithrombin III, proteins C and S).

B. Clinical Features

1. Symptoms (see also Clinical Pearl 1-11)
   a. Intermittent claudication
      - Cramping leg pain that is reliably reproduced by same walking distance (distance is very constant and reproducible)
      - Pain is completely relieved by rest

   b. Rest pain (continuous)
      - Usually felt over the distal metatarsals, where the arteries are the smallest
      - *Often prominent at night*—awakens patient from sleep
      - Hanging the foot over side of the bed or standing relieves pain—extra perfusion to ischemic areas due to gravity
      - Rest pain is always worrisome—suggests severe ischemia such that frank gangrene of involved limb may occur in the absence of intervention
2. Signs
   a. Diminished or absent pulses, muscular atrophy, decreased hair growth, thick toenails, and decreased skin temperature

   b. Ischemic ulceration (usually on the toes)
      - Localized skin necrosis
      - Secondary to local trauma that does not heal (due to ischemic limb)
      - Tissue infarction/gangrene in end-stage disease

   c. Pallor of elevation and rubor of dependency (in advanced disease)

Quick HIT

- Femoral or popliteal disease causes calf claudication.
- Aortoiliac occlusive disease causes buttock and hip claudication (in addition to the calves).

Quick HIT

Patients with calcified arteries (especially those with DM) have false ABI readings (vessels are not compressible).

C. Diagnosis

1. Ankle-to-brachial index (ABI): Ratio of the systolic BP at the ankle to the systolic BP at the arm
   a. Normal ABI is between 0.9 and 1.3
   b. ABI >1.3 is due to noncompressible vessels and indicates severe disease
   c. Claudication usually when ABI <0.7
   d. Rest pain usually when ABI <0.4
2. Pulse volume recordings
   a. Excellent assessment of segmental limb perfusion
   b. Pulse wave forms represent the volume of blood per heart beat at sequential sites down the leg
   c. A large wave form indicates good collateral blood flow
   d. Noninvasive using pressure cuffs
3. Arteriography (contrast in vessels and radiographs)
   a. Gold standard for diagnosing and locating PAD

Quick HIT

Diabetic patients have an amputation rate four times greater than that of nondiabetic patients.

D. Treatment

1. Conservative management for intermittent claudication.
   a. **Smoking cessation is essential.** Smoking is linked to progression of atherosclerosis and causes vasoconstriction (further decreasing blood flow)
   b. Graduated exercise program: Walk to point of claudication, rest, and then continue walking for another cycle
   c. Foot care (especially important in diabetic patients)
   d. Atherosclerotic risk factor reduction (control of hyperlipidemia, HTN, weight, diabetes, and so on)
   e. Avoid extremes of temperature (especially extreme cold)
   f. Aspirin along with clopidogrel has shown slight improvements in symptom relief. They are often used in these patients for stroke/MI prevention
   g. Cilostazol is a PDE inhibitor which acts both by suppressing platelet aggregation and by directly dilating arterioles
2. Surgical treatment
   a. Indications: Rest pain, ischemic ulcerations (tissue necrosis), severe symptoms refractory to conservative treatment that affect quality of life or work
   b. Options
      - Angioplasty—balloon dilation with or without stenting. Given the minimal risks and good chance of symptomatic relief for patients, this may be performed one or more times before a bypass is done. Not useful when performed on below-the-knee lesions
      - Surgical bypass grafting—has a 5-year patency rate of 70% (immediate success rate is 80% to 90%).

Acute Arterial Occlusion

A. General Characteristics

1. Acute occlusion of an artery, usually caused by embolization. The common femoral artery is the most common site of occlusion. Less commonly, in situ thrombosis is the cause.
2. Sources of emboli

a. Heart (85%)
  - AFib is the most common cause of embolus from the heart
  - Post-MI
  - Post arterial procedure (i.e., coronary angiogram, peripheral angiogram)
  - Endocarditis
  - Myxoma

b. Aneurysms

c. Atheromatous plaque

B. Clinical Features of Acute Limb Ischemia (Remember the Six Ps)

1. **P**ain—acute onset. The patient can tell you precisely when and where it happened. The pain is very severe, and the patient may have to sit down or may fall to the ground (Table 1-4)
2. **P**allor
3. **P**olar (cold)
4. **P**aralysis
5. **P**aresthesias
6. **P**ulselessness (use Doppler to assess pulses)

TABLE 1-4 PAD versus Acute Arterial Occlusion

	Clinical Features	Diagnosis	Treatment
Peripheral arterial disease	Intermittent claudication, rest pain, decreased pulses, ischemic ulcers	Arteriogram	Intermittent claudication—conservative treatment Rest pain—surgery
Acute arterial occlusion	Six Ps—pallor, pain, pulselessness, paresthesias, paralysis, polar (cold)	Arteriogram	Anticoagulation, emergent surgery

C. Diagnosis

1. Angiogram (CTA vs. invasive angiogram) to define site of occlusion
2. ECG to look for MI, AFib

3. Echocardiogram for evaluation of cardiac source of emboli—valves, thrombus, shunts

D. Treatment

1. Main goal: Assess viability of tissues to salvage the limb.
2. Skeletal muscle can tolerate 6 hours of ischemia; perfusion should be reestablished within this time frame.
3. Immediately anticoagulate with IV heparin.
4. Emergent surgical embolectomy is indicated via cutdown and Fogarty balloon. Bypass is reserved for embolectomy failure.
5. Thrombolytics can also be infused intraarterially. Double-blind trials comparing intraarterial thrombolytics such as recombinant urokinase to surgery showed mixed results.
6. Treat any complications such as compartment syndrome that may occur.

Quick HIT

The Fogarty balloon catheter is used for embolectomy—the catheter is inserted, the balloon is inflated, and the catheter is pulled out—the balloon brings the embolus with it.

Cholesterol Embolization Syndrome

- This syndrome is due to "showers" of cholesterol crystals originating from a proximal source (e.g., atherosclerotic plaque), most commonly the abdominal aorta, iliacs, and femoral arteries.
- It is often triggered by a surgical or radiographic intervention (e.g., arteriogram), or by thrombolytic therapy.
- It presents with small, discrete areas of tissue ischemia, resulting in blue/black toes, renal insufficiency, and/or abdominal pain or bleeding (the latter is due to intestinal hypoperfusion).
- Treatment is supportive. Anticoagulation not suggested unless other indication exists (most of the occlusion is atheroembolic debris, not thrombus). Control BP. Amputation or surgical resection is only needed in extreme cases.

Deep Venous Thrombosis

A. General Characteristics

1. Cause: *Virchow triad* (endothelial injury, venous stasis, hypercoagulability) gives rise to venous thrombosis (see also Table 1-5)
2. Risk factors
   a. Age >60 years
   b. Malignancy
   c. Prior history of deep venous thrombosis (DVT), PE, or varicose veins
   d. Hereditary hypercoagulable states (e.g., factor V Leiden, proteins C and S deficiency, antithrombin III deficiency)
   e. Prolonged immobilization or bed rest
   f. Cardiac disease, especially CHF
   g. Obesity
   h. Major surgery, especially surgery of the pelvis (orthopedic procedures)
   i. Major trauma
   j. Pregnancy, oral contraceptives/estrogen use

TABLE 1-5 Diseases of the Venous System

Disease	Clinical Features	Diagnosis	Treatment
Superficial thrombophlebitis	Local tenderness, erythema along the course of a superficial vein	Clinical diagnosis	Analgesics, monitor for spread or cellulitis
Chronic venous insufficiency	Aching of lower extremities, worse at end of day; relieved by elevation of legs and worsened by recumbency; edema, pigmentation, ulcers	Clinical diagnosis	Leg elevation, avoid long periods of standing, elastic stockings; if ulcers develop, Unna boots, wet-to-dry dressings
Deep venous thrombosis	Usually asymptomatic; calf pain may be present	Duplex, D-dimer	Anticoagulation

B. Clinical Features

1. Clinical presentation may be subtle
2. Classic findings (all have very low sensitivity and specificity)
   a. Lower extremity pain and swelling (worse with dependency/walking, better with elevation/rest)
   b. *Homans sign* (calf pain on ankle dorsiflexion)
   c. Palpable cord
   d. Fever

Quick HIT

Only 50% of patients with the classic DVT findings have a DVT, and only 50% of patients with documented DVT have the classic findings.

C. Diagnosis

1. Available studies
   a. Doppler analysis and Duplex ultrasound
      - Initial test for DVT; noninvasive, but highly operator dependent
      - High sensitivity and specificity for detecting proximal thrombi (popliteal and femoral), not so for distal (calf vein) thrombi

   b. Venography
      - Most accurate test for diagnosis of DVT of calf veins
      - Invasive and infrequently used
      - Allows visualization of the deep and superficial venous systems, and allows assessment of patency and valvular competence

   c. Impedance plethysmography
      - A noninvasive alternative to Doppler ultrasound
      - Blood conducts electricity better than soft tissue, so electrical impedance decreases as blood volume increases
      - High sensitivity for proximal DVT, but not for distal DVT (calf veins)
      - Poor specificity because there is a high rate of false positives
      - As accurate as Doppler, but less operator dependent

   d. D-dimer testing

- Has a very high sensitivity (95%), but low specificity (50%); can be used to rule out DVT when combined with Doppler and clinical suspicion

2. Interpretation of diagnostic tests
   a. Low or moderate pretest probability: D-dimer can be used to rule out DVT, or if elevated proceed to ultrasound to rule in or rule out DVT
   b. High pretest probability: proceed to ultrasound. If negative, consider D-dimer testing, repeating ultrasound in a week, or additional imaging studies of clot could be more proximal

D. Complications

1. Pulmonary embolism (PE) can originate from the iliofemoral, pelvic, calf, ovarian, axillary, subclavian, and internal jugular veins, as well as the inferior vena cava and cavernous sinuses of the skull—see Chapter 2 for discussion on PE
2. Postthrombotic syndrome (chronic venous insufficiency)
   a. Occurs in approximately half of all patients with acute DVT
   b. Residual venous obstruction and valvular incompetence lead to ambulatory HTN (see section Chronic Venous Insufficiency)
3. Phlegmasia cerulea dolens (painful, blue, swollen leg)
   a. Occurs in extreme cases of DVT—indicates that major venous obstruction has occurred. Often associated with malignancy causing hypercoagulable state.
   b. Severe leg edema compromises arterial supply to the limb, resulting in impaired sensory and motor function.
   c. Venous thrombectomy is indicated.

E. Treatment

1. Anticoagulation
   a. Prevents further propagation of the thrombus
   b. Multiple options: DOACs, LMWH, or warfarin
2. Thrombolytic therapy (streptokinase, urokinase, tissue plasminogen activator [tPA])
   a. Speeds up the resolution of clots
   b. Indicated mainly for patients with massive PE who are hemodynamically unstable (hypotension with SBP <90 mm Hg), and

with no contraindications for thrombolytics

c. High risk of intracranial hemorrhage with tPA (1% to 2%)

3. Inferior vena cava filter placement
   a. Indicated when there is a contraindication to anticoagulation (e.g., intracranial hemorrhage). All filters should be removed when the contraindication to anticoagulation has resolved.
   b. Effective only in preventing PE, not DVT

Quick HIT

Low–Molecular-Weight Heparin
- Has longer half-life than unfractionated heparin and can be dosed once daily or BID
- Can be given on outpatient basis
- No need to follow aPTT levels
- Lower risk of heparin-induced thrombocytopenia (HIT) compared to unfractionated heparin

Chronic Venous Insufficiency (Venous Stasis Disease)

A. General Characteristics

1. Also referred to as postphlebitic syndrome
2. CVI may involve the superficial, deep, or both venous systems
3. Anatomy
   a. The lower extremity venous system consists of three systems: Deep, superficial, and perforating systems. Valves exist in all three systems, preventing retrograde blood flow.
   b. The perforating veins connect the superficial and deep systems. Valves allow flow from superficial to deep, but not vice versa.
4. Pathophysiology
   a. History of DVT is the underlying cause in many cases (such a history might not be documented). This has two major effects:
      - It causes destruction of venous valves in the deep venous system. Valvular incompetence results in gravitational pressure of the blood column to be transmitted to ankles.

- Valves in the perforator veins are also damaged secondary to the chronically elevated deep venous pressure, inhibiting transmission of blood from superficial to deep, as normally occurs.

b. Leads to *ambulatory venous HTN,* which has two undesirable effects:
   - Interstitial fluid accumulation, resulting in edema.
   - Extravasation of plasma proteins and RBCs into subcutaneous tissues, resulting in brawny induration and pigmentation (a brown-black color) of skin.

c. Eventually leads to reduced local capillary blood flow and hypoxia of tissues.
   - Even mild trauma may precipitate tissue death and ulcer formation.
   - Venous ulcers usually develop medially from the instep to above the ankle, overlying an incompetent perforator vein.

Quick HIT

Many patients with a history of DVT eventually develop CVI (80%).

B. Clinical Features

1. Swelling of the lower leg
   a. When chronic, causes an aching or tightness feeling of the involved leg; often worse at the end of the day
   b. Symptoms are worsened by periods of sitting or inactive standing
   c. Leg elevation provides relief of symptoms (the opposite is true in arterial insufficiency)
2. Chronic changes include:
   a. Skin changes
      - Skin becomes thin, atrophic, shiny, and cyanotic
      - Brawny induration develops with chronicity

   b. Venous ulcers
      - Less painful than ulcers associated with arterial insufficiency
      - Usually located just above the medial malleolus
      - Often rapidly recur

Quick HIT

Ulcer formation is directly proportional to the amount of swelling present.

Quick HIT

When superficial thrombophlebitis occurs in different locations over a short period of time, think of *migratory superficial thrombophlebitis* (secondary to occult malignancy, often of the pancreas—Trousseau syndrome).

C. Treatment

1. Before the development of ulcers, strict adherence to the following controls stasis sequelae in most patients.
   a. Leg elevation: Periods of leg elevation during the day and throughout the night to a level above the heart.
   b. Avoiding long periods of sitting or standing.
   c. Heavy-weight elastic stockings (knee-length) are worn during waking hours.
2. If ulcers develop, management also entails:
   a. Wound care, external compression stockings, etc.

Superficial Thrombophlebitis

A. General Characteristics

1. Virchow triad is again implicated (but pathophysiology is not entirely clear)
2. In upper extremities, usually occurs at the site of an IV infusion
3. In lower extremities, usually associated with *varicose veins* (in the greater saphenous system)—secondary to static blood flow in these veins

Quick HIT

Two conditions that should not be confused with superficial thrombophlebitis are cellulitis and lymphangitis. In these conditions, swelling and erythema are more widespread, and there is no palpable, indurated vein.

B. Clinical Features

1. Pain, tenderness, induration, and erythema along the course of the vein
2. A tender cord may be palpated

C. Treatment

1. *No anticoagulation* is required—rarely causes PE. Only if thrombus extends into the deep system.
2. Localized thrombophlebitis—a mild analgesic (aspirin or NSAIDs) elevation, and hot compresses; continue activity.
3. Suppurative thrombophlebitis—septic phlebitis is usually due to infection of an IV cannula. Redness extends beyond the area of the vein and purulent drainage may be present. Remove the cannula and administer systemic antibiotics.

Cardiac Neoplasms

- Primary tumors of the heart are rare (typically less than 0.1% of the general population).
- Metastases from other primary tumors are more common (75% of cardiac neoplasms). Sites of these primary tumors include the lung, breast, skin, kidney, lymphomas, and Kaposi sarcoma in patients with AIDS.

Atrial Myxoma

- An atrial myxoma is a benign gelatinous growth, usually pedunculated and arising from the interatrial septum of the heart in the region of the fossa ovalis. It is the most common primary cardiac neoplasm.
- Although benign, atrial myxomas can embolize, leading to metastatic disease, or can cause relative valvular dysfunction.

- The majority of myxomas are sporadic, but autosomal-dominant transmission has been noted.
- Prototypically present with fatigue, fever, syncope, palpitations, malaise, and a low-pitched diastolic murmur that changes character with changing body positions *(diastolic plop)*.
- Treatment: Surgical excision.

Shock

Basics of Shock

A. General Characteristics

1. Shock is hypotension causing end-organ hypoperfusion. It is a medical emergency that needs to be corrected right away, before the condition becomes irreversible.
2. Presents with tachycardia, a decrease in BP, and malfunction of underperfused organ systems, most notably:
   a. Lactic acidosis
   b. Renal (anuria/oliguria)
   c. CNS dysfunction (altered mentation)
3. Shock is characterized by its effect on cardiac output, SVR, and volume status (volume status is assessed via jugular venous pressure or pulmonary capillary wedge pressure [PCWP]). The hemodynamic changes associated with different types of shock are set forth in Table 1-6.
4. There are four main categories of shock:
   - Hypovolemic (poor intake or excessive loss of fluids)
   - Cardiogenic (poor pumping function or circulatory overload)
   - Distributive (low SVR and high cardiac output states which include septic, anaphylactic, neurogenic shock, and severe hepatic failure)
   - Obstructive (i.e., massive PE, cardiac tamponade, tension pneumothorax)

TABLE 1-6 Hemodynamic Changes in Shock States

Shock	Cardiac Output	SVR	PCWP
Cardiogenic	↓	↑	↑
Hypovolemic	↓	↑	↓
Distributive			
Neurogenic	↓	↓	↓
Septic	↑	↓	↓
Obstructive	↓	↑	Variable

***Quick* HIT**

The following signs and symptoms are common to all forms of shock:
- Hypotension
- Oliguria
- Tachycardia
- Altered mental status

B. Initial Approach to a Patient in Shock

1. A focused history and physical examination to determine possible cause of shock.
   a. Fever, warm extremities, and a possible site of infection suggest septic shock.
   b. Trauma, GI bleeding, vomiting, or diarrhea suggests hypovolemic shock.
   c. If signs of volume overload and cool, clammy extremities are present, this suggests cardiogenic shock.
   d. If spinal cord injury or neurologic deficits are present, neurogenic shock is likely.
   e. If the patient has been exposed to a new medication or allergen, consider anaphylactic shock.
2. Initial steps: Simultaneously stabilize the patient hemodynamically and determine the cause of shock.

a. Initiate workup: CBC, BMP, infectious workup (blood and urine cultures, chest imaging), ECG, consider bedside echocardiography if concern for cardiogenic shock.
b. Establish two large-bore IVs if fluid resuscitation indicated, and consider a central line, and an arterial line if vasopressors indicated.
c. A fluid bolus (multiple liters of normal saline or lactated Ringer solution) should be given in most cases (except cardiogenic shock, as more volume will worsen it).
d. Continuous pulse oximetry.
e. Vasopressors (such as norepinephrine) may be given if the patient remains hypotensive despite fluids.
f. If the diagnosis is still in question after the above tests, a pulmonary artery catheter (Swan–Ganz catheter) may help in diagnosis.

C. Treatment

1. ABCs (airway, breathing, and circulation) should be addressed for all patients in shock.
2. Specific treatment is described below for each type of shock. With the exception of cardiogenic (and sometimes neurogenic) shock, a generous amount of IV fluid is usually required to resuscitate the patient. The more advanced the stage of shock, the greater the fluid (and blood) requirement.

Cardiogenic Shock

A. General Characteristics

1. Occurs when heart is unable to generate a cardiac output sufficient to maintain tissue perfusion
2. Can be defined as a systolic BP <90 with urine output <20 mL/hr and adequate left ventricular filling pressure (LV filling pressure usually elevated in cardiogenic shock)

B. Causes

1. After acute MI—most common cause
2. Decompensated heart failure
3. After cardiac arrest

4. Arrhythmias
5. Mechanical abnormalities (valvular defects, ventricular septal defect)

C. Clinical Features

1. Ill-appearing patients with low cardiac output, markedly increased SVR (with cool extremities due to vasoconstriction)
2. Engorged neck veins—JVP elevated
3. Pulmonary congestion

Quick HIT

Note that jugular venous pulse is only elevated in cardiogenic and obstructive shock.

D. Diagnosis

1. ECG—look for signs of ischemia (i.e., ST-segment changes) or arrhythmia (ventricular or atrial tachyarrhythmia).
2. Echocardiogram—can diagnose a variety of mechanical complications of MI, identify valve disease, estimate EF, look for pericardial effusion, etc.
3. Hemodynamic monitoring with a Swan–Ganz catheter may be indicated: PCWP, pulmonary artery pressure, cardiac output, CI, SVR —keep cardiac output >4 L/min, CI >2.2, PCWP <18 mm Hg.

E. Treatment

1. ABCs
2. Identify and treat underlying cause
   a. Acute MI
      - Standard treatment (see MI section)
      - Emergent revascularization with PCI (or CABG) has been shown to improve survival
   b. If cardiac tamponade, pericardiocentesis/surgery
   c. Surgical correction of valvular abnormalities
   d. Treatment of arrhythmias

3. Preload reduction for patients with volume overload: Loop diuretics, dialysis if renal failure, nitroglycerin (though this can worsen hypotension)
4. Vasopressors and inotropes
   a. Norepinephrine is typically started as the first line pressor for hypotension. The SOAP II trial found that for patients with cardiogenic shock, dopamine had higher 28-day mortality compared to norepinephrine
   b. Dobutamine or milrinone (inotropes) can be used to increase inotropy and simultaneously decrease afterload (SVR), enhancing cardiac output
5. Afterload reduction
   a. IV agents such as sodium nitroprusside can be used to quickly reduce afterload. There is a risk of hypotension with rapidly increasing the dose.
   b. Oral agents such as hydralazine and captopril can reduce afterload, are short acting.
6. IV fluids are likely to be harmful if left ventricular pressures are elevated. Patients usually need diuretics.
7. IABPs can be used for hemodynamic support (see Clinical Pearl 1-12). Effects include:
   a. Decreased afterload
   b. Increased cardiac output
   c. Decreased myocardial oxygen demand
8. More advanced mechanical support devices such as extracorporeal membrane oxygenation and left ventricular assist devices (percutaneously or surgically implanted) can be used for patients with more severe shock, and are outside the scope of this text.

CLINICAL PEARL 1-12

Intraaortic Balloon Pump

- A device that gives "mechanical support" to a failing heart—it works opposite to the normal pumping action of the heart, that is, it serves to "pump" during diastole and "relax" during systole.
- A balloon catheter is positioned in the descending thoracic aorta just distal to the subclavian artery. **It facilitates ventricular emptying by deflating just before the onset of systole *(reducing afterload)* and increases coronary perfusion by inflating at the onset of diastole (increasing diastolic pressure).**
- *The net effect is enhanced myocardial oxygenation and increased cardiac output.*
- Indications are angina refractory to medical therapy, mechanical complications of MI, cardiogenic shock, low cardiac output states, and as a bridge to surgery in severe AS.

Quick HIT

- Compensatory mechanisms begin to fail when more than 20% to 25% of blood volume is lost.
- If CVP is low, hypovolemic shock is most likely present.

Hypovolemic Shock

A. General Characteristics

1. Primary pathophysiologic events: Decreased circulatory blood volume leads to decreased preload and cardiac output. Compensatory increase in SVR
2. The rate of volume loss is very important. The slower the loss, the greater the effectiveness of compensatory mechanisms. Acute loss is associated with higher morbidity and mortality
3. Patients with significant medical comorbidities (especially cardiac) may be unable to compensate physiologically in the early stages of hypovolemic shock
4. There are four "classes" of hypovolemic shock, based on the severity of volume loss (Table 1-7)
5. Causes

a. Hemorrhage
- Trauma
- GI bleeding
- Retroperitoneal

b. Nonhemorrhagic
- Voluminous vomiting
- Severe diarrhea
- Severe dehydration for any reason
- Burns
- Third-space losses in bowel obstruction

TABLE 1-7 Hemodynamic Changes in Hypovolemic Shock

Class	Blood Volume Lost (%)	Pulse (↑)	Systolic BP (↓)	Pulse Pressure (↓)	Capillary Refill (↓)	Respiratory Rate (↑)	CNS	Urine Output (↓)
I	10–15	Normal	Normal	Normal	Normal	Normal	Normal	Normal
II	20–30	>100	Normal	Decreased	Delayed	Mild tachypnea	Anxious	20–30 mL/hr
III	30–40	>120 weak	Decreased	Decreased	Delayed	Marked tachypnea	Confused	20 mL/hr
IV	>40	>140 nonpalpable	Marked decrease	Marked decrease	Absent	Marked tachypnea	Lethargic, coma	Negligible

B. Diagnosis

If the diagnosis is unclear from the patient's vital signs and clinical picture, a central venous line or a pulmonary artery catheter can give invaluable information for hemodynamic monitoring: Decreased CVP/PCWP, decreased cardiac output, increased SVR (see Table 1-6).

C. Treatment

1. Airway and breathing—patients in **severe** shock and circulatory collapse generally require intubation and mechanical ventilation.
2. Circulation
   a. If hemorrhage is the cause, early resuscitation with fluids and blood products (e.g., massive transfusion protocols) followed by procedural intervention to stop the bleeding. Examples include open surgical exploration for an abdominal bleed, GI endoscopy for an

upper GI bleed, IR angiography with embolization of a bleeding vessel, and so on.

b. For nonhemorrhagic shock, blood is not necessary. Crystalloid solution with appropriate electrolyte replacement is adequate.

Quick HIT

Monitoring urine output is a useful indicator of the effectiveness of treatment. A pulmonary artery catheter and/or central venous line, if available, are very helpful in monitoring as well.

Septic Shock

A. General Characteristics

1. Septic shock is defined as hypotension induced by sepsis that persists despite adequate fluid resuscitation. This results in hypoperfusion and can ultimately lead to multiple organ system failure and death.
2. Common causes include (but are not limited to) pneumonia, urinary tract infection, meningitis, abscess formation, cholangitis, cellulitis, and peritonitis.
3. Clinically, there is a progression from systemic inflammatory response syndrome (SIRS) to sepsis, to septic shock, to multiorgan dysfunction syndrome—see Clinical Pearl 1-12.
4. Pathophysiology
   a. There is a severe decrease in SVR secondary to peripheral vasodilation. Extremities are often warm due to vasodilation.
   b. Cardiac output is normal or increased (due to maintenance of stroke volume and tachycardia).
   c. EF is decreased secondary to a reduction in contractility.
5. Can be complicated by adult respiratory distress syndrome, ATN, DIC, multiple organ failure, or death.

Quick HIT

Septic (and other types of distributive shock) are associated with severe peripheral vasodilatation (flushing, warm skin).

Hypovolemic, cardiogenic, and obstructive shock are associated with peripheral vasoconstriction (cool skin).

B. Clinical Features

1. Manifestations related to cause of sepsis (e.g., pneumonia, urinary tract infection, peritonitis)
2. Signs of SIRS (see Clinical Pearl 1-13)
3. Signs of shock (hypotension, oliguria, lactic acidosis)
4. Patient may have a **fever** or may be **hypothermic** (hypothermia is more common in the very young, elderly, debilitated, and immunocompromised)

C. Diagnosis

1. Septic shock is essentially a clinical diagnosis.
2. A source of infection can aid in diagnosis, but there may be no confirmed source in some cases.

D. Treatment

1. Fluid administration to increase mean BP (initial bolus is usually 30 cc/kg of body weight).
2. Obtain cultures prior to starting antibiotics. Start IV antibiotics (broad spectrum) at maximum dosages. Antibiotics for more rare organisms or antifungal medications may be required if there is no clinical response or if suspicion for an atypical organism (i.e., immunocompromised). If cultures are positive, antibiotics can be narrowed based on sensitivity testing.
3. Surgical drainage if necessary.
4. Vasopressors (norepinephrine, vasopressin, phenylephrine) may be used if hypotension persists despite aggressive IV fluid resuscitation.

Quick HIT

Septic shock is the most common cause of death in the ICU.

CLINICAL PEARL 1-13

Systemic Inflammatory Response Syndrome (SIRS)

SIRS

SIRS is characterized by *two or more* of the following:

- Fever (>38 °C) or hypothermia (<36 °C)
- Hyperventilation (rate >20 bpm) or $PaCO_2$ <32 mm Hg
- Tachycardia (>90 bpm)
- Increased WBC count (>12,000 cell/hpf, <4,000 cells/hpf, or >10% band forms)

Sepsis

- When have a suspected source of infection and SIRS is present

Septic Shock

- Hypotension induced by sepsis persisting despite adequate fluid resuscitation

Multiple Organ Dysfunction Syndrome (MODS)

- Altered organ function in an acutely ill patient, usually leading to death

Neurogenic Shock

A. General Characteristics

1. Neurogenic shock results from a failure of the sympathetic nervous system to maintain adequate vascular tone (sympathetic denervation)
2. Causes include spinal cord injury, severe head injury, spinal anesthesia, pharmacologic sympathetic blockade
3. Characterized by peripheral vasodilation with decreased SVR

B. Clinical Features

1. Warm, well-perfused skin

2. Urine output low or normal
3. Bradycardia and hypotension (but tachycardia can occur)
4. Cardiac output is decreased, SVR low, PCWP low to normal

C. Treatment

1. Judicious use of IV fluids as the mainstay of treatment
2. Vasoconstrictors to restore venous tone, but cautiously
3. Supine or Trendelenburg position
4. Maintain body temperature

Obstructive Shock

A. General Characteristics

1. Caused by an obstruction of circulation. Most commonly due to massive PE or limited filling of the heart due to extrinsic pressure from pericardium (cardiac tamponade) or thoracic cavity (tension pneumothorax).
2. Cardiac output limited by obstruction, SVR makes a compensatory increase to maintain systemic blood pressure.
3. Usually manifests with elevated JVP due to limited filling of right ventricle or obstruction of pulmonary circulation by PE.
4. Treatment requires diagnosis of underlying disease. Cardiac tamponade and tension pneumothorax are clinical diagnoses that can be made at bedside.
5. Supportive treatment usually involves giving fluid and/or vasopressors to maintain blood pressures until definitive therapy can be given.
6. Cardiac tamponade: Requires pericardiocentesis or pericardial window.
7. Tension pneumothorax: Requires needle thoracostomy followed by chest tube placement.
8. Massive PE: Requires thrombolysis (systemic or catheter-directed tPA) or thrombectomy.

Syncope

A. General Characteristics

1. Syncope refers to a transient loss of consciousness/postural tone secondary to acute decrease in cerebral blood flow. It is characterized by rapid recovery of consciousness without resuscitation.
2. Seizure is not a cause of syncope, it produces acute encephalopathy but by a different mechanism.

Quick HIT

Prognosis of syncope is generally good, unless cardiac disease is the underlying cause.

B. Causes

1. Cardiac
   a. Cardiac syncope is usually sudden and without prodromal symptoms—for example, the patient's face hits the floor.
   b. A cardiac cause of syncope is the most important to consider and rule out, since syncope may be the first manifestation of a life-threatening cardiac condition.
   c. Causes
      - Arrhythmias (e.g., sick sinus syndrome, ventricular tachycardia, AV block, rapid supraventricular tachycardia).
      - Obstruction of blood flow (AS, HCM, pulmonary HTN, atrial myxoma, etc.).
      - PE can theoretically cause sudden obstruction of blood flow and temporary cerebral hypoperfusion, leading to syncope. The PESIT trial in 2016 found that for high-risk patients admitted to the hospital for syncope, one in six patients were found to have a PE (though this shows correlation, not causation).
2. Vasovagal syncope ("neurocardiogenic," or "reflex syncope")
   a. Most **common cause of syncope;** may account for up to 50% of all cases of syncope
   b. Most people have one episode, but for some it is a recurrent problem

c. Clues to diagnosis
- Emotional stress, pain, fear, extreme fatigue, or claustrophobic situations as precipitating factors.
- Premonitory symptoms (pallor, diaphoresis, lightheadedness, nausea, dimming of vision, roaring in the ears).
- Can occur at any age, but if the first episode is after age 40, be reluctant to make this diagnosis.
- Tilt-table study can reproduce the symptoms in susceptible people.

d. Pathophysiology
- Normally, standing up causes blood to pool in the lower extremities (leading to a decrease in cardiac output, stroke volume, and BP). These changes are compensated for by increased sympathetic tone (leading to vasoconstriction and tachycardia), and decreased parasympathetic tone.
- In patients with vasovagal syncope, the compensatory response is interrupted in a few minutes by a paradoxical withdrawal of sympathetic stimulation and a replacement by enhanced parasympathetic (vagal) activity. This leads to an inappropriate bradycardia, vasodilation, marked decrease in BP, and cerebral perfusion.

e. Treatment
- Can usually be reversed by assuming the supine posture and elevating the legs.
- β-Blockers and disopyramide.
- Prognosis is excellent (there is no heart disease or arrhythmias).

f. Prevention—avoid circumstances that precipitate attack

Quick HIT

Vasovagal and orthostatic syncope occur when the patient is upright (sitting up or standing). They do not occur when the patient is recumbent.

3. Orthostatic hypotension

a. Causes include intravascular volume depletion, autonomic insufficiency (e.g., primary autonomic insufficiency from Parkinson

disease, or secondary from diabetes), age-related loss of vasomotor reflexes, and drugs.

b. Common in elderly people; diabetics (autonomic neuropathy); patients taking ganglionic-blocking agents, vasodilators, diuretics.

c. Sudden standing and prolonged standing are the precipitating causes.

d. It is also associated with premonitory symptoms (lightheadedness, nausea, etc.).

e. Treat with increased sodium intake and fluids. Consider fludrocortisone if recurrent. Remember to treat other underlying causes if identified (such as withdrawal of offending medication).

4. Severe cerebrovascular disease

a. A rare cause of syncope.

b. A TIA involving the **vertebrobasilar** circulation may lead to syncope ("drop attacks").

c. One practically never sees dizziness (or vertigo) in isolation with vertebrobasilar insufficiency—there will always be other deficits as well.

***Quick* HIT**

If syncope occurs with exertion, assess for potentially life-threatening causes such as HCM or AS.

***Quick* HIT**

Syncope is uncommon in setting of a stroke, unless the vertebrobasilar system is involved.

C. Diagnosis

1. First, attempt to rule out conditions that are life threatening (e.g., MI, hemorrhage, and arrhythmias) (Figure 1-16).

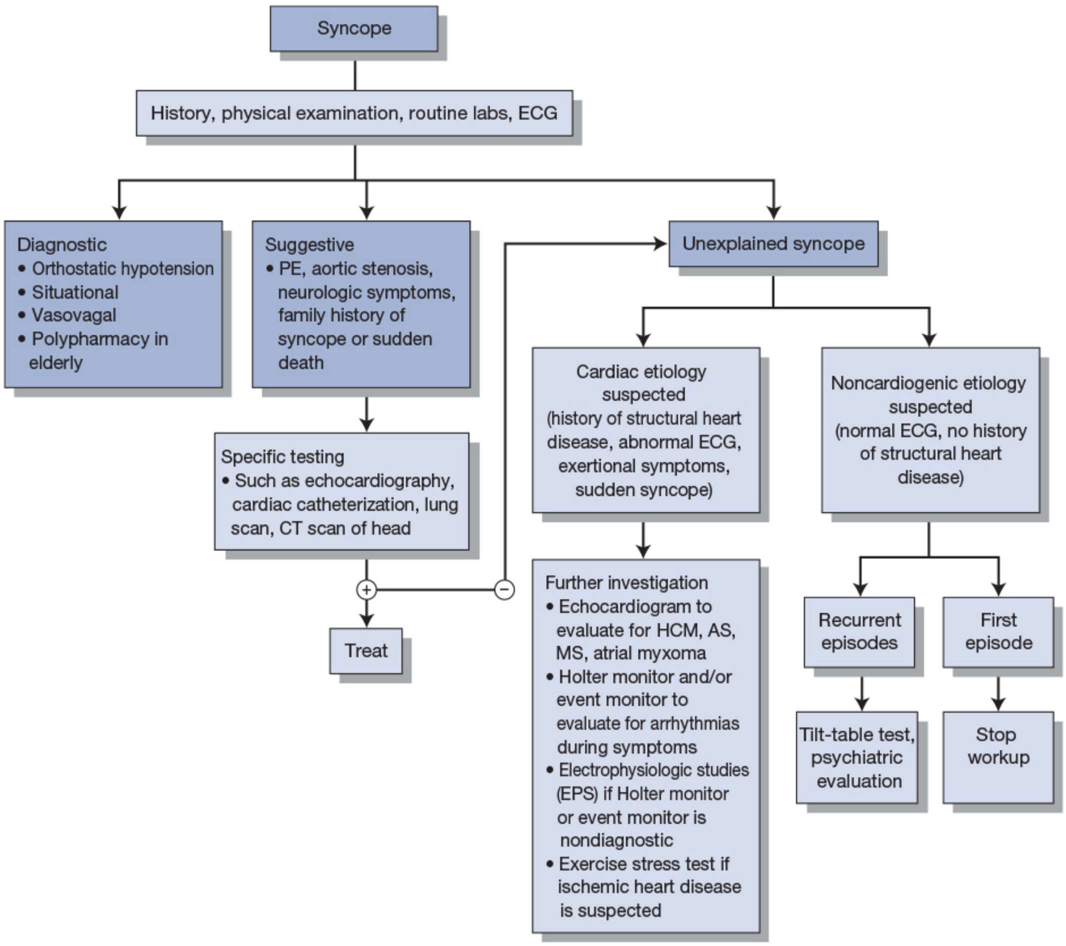


FIGURE 1-16 Syncope flowchart.
(From Linzer M, Yang EH, Estes NA III, et al. Clinical Guideline: Diagnosing syncope: Part 1: Value of history, physical examination, and electrocardiography. *Ann Intern Med* 1997;126(12):989–966. Copyright © 1997 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.)

Quick HIT

Evaluating Syncope

- The most important factors in decision making in syncope patients are presence/absence of structural heart disease and abnormal ECG.

2. The main goal is to **differentiate between cardiac and noncardiac etiologies,** because the prognosis is poorest for those with underlying heart disease.

3. History
   a. Three key elements need to be determined: events before, during, and after the syncopal episode.
   b. Check the patient's medications—this is especially important in elderly patients.
   c. Seek reports from witnesses of the syncopal event.
4. Physical examination (priority given to cardiovascular system)
   a. BP and pulse measurements in supine, sitting, and standing positions (orthostatic vital signs)
   b. Mental status (postictal state)
   c. Murmurs (AS, HCM)
5. Diagnosis
   a. **ECG** should be obtained in all patients with syncope, and may identify life-threatening causes (ventricular tachycardia, other arrhythmias, ischemia).
   b. CBC, metabolic panel, and other labs based on the history and physical may be appropriate.
   c. Echocardiography if structural heart disease is suspected.
   d. Additional diagnostic tests may be indicated, and include ambulatory ECG monitoring, exercise testing, carotid sinus massage, neurologic studies such as EEG or neurovascular imaging, and electrophysiologic studies. Tilt-table testing was frequently used to diagnose vasovagal syncope in the past, but is now controversial.
   e. Risk stratification tools (e.g., San Francisco Syncope Rule) can help in the decision of whether or not to admit the patient to the hospital for further evaluation, or if they can be discharged home with follow-up.

Diseases of the Pulmonary System

2

Kelley Chuang

Obstructive Lung Diseases

Chronic Obstructive Pulmonary Disease

A. General Characteristics

1. There are two classic types of chronic obstructive pulmonary disease (COPD): **chronic bronchitis** and **emphysema** (see Table 2-1 and Clinical Pearl 2-1)
   a. Chronic bronchitis is a clinical diagnosis: chronic cough productive of sputum for at least 3 months per year for at least 2 consecutive years, when other causes of chronic cough have been excluded.
   b. Emphysema is a pathologic diagnosis: permanent enlargement of air spaces distal to terminal bronchioles due to destruction of alveolar walls without fibrosis.
   c. **The two often coexist.** Pure emphysema or pure chronic bronchitis is rare.
   d. There is also possible overlap between asthma and COPD, although there is no consensus on the definition. Some may have features of both diseases.
   e. **COPD is a leading cause of death in the United States.**

Quick HIT

Pathology

Centrilobular emphysema:

- Most common type, seen in smokers (rarely in nonsmokers)
- Destruction limited to respiratory bronchioles (proximal acini) with little change in distal acini
- Predilection for upper lung zones

Panlobular emphysema:

- Seen in patients with α_1-antitrypsin deficiency
- Destruction involves both proximal and distal acini
- Predilection for lung bases

2. Risk factors and causes
   a. Tobacco smoke (indicated in almost 90% of COPD cases)
   b. α_1-Antitrypsin deficiency—risk is even worse in combination with smoking
   c. Environmental factors (e.g., exposure to second-hand smoke, fumes, or dust)
   d. Chronic asthma-COPD overlap syndrome
3. Pathogenesis
   a. Chronic bronchitis
      - Excess mucus production narrows the airways; patients often have a productive cough.
      - Inflammation and scarring in airways, enlargement in mucous glands, and smooth muscle hyperplasia lead to obstruction.
   b. Emphysema
      - Destruction of alveolar walls is due to relative excess in protease (elastase) activity, or relative deficiency of antiprotease (α_1-antitrypsin) activity in the lung. Elastase is released from polymorphonuclear neutrophils (PMNs) and macrophages and digests human lung. This is inhibited by α_1-antitrypsin.
      - Tobacco smoke increases the number of activated PMNs and macrophages, inhibits α_1-antitrypsin, and increases oxidative stress on the lung by free-radical production.

Quick HIT

In COPD:

- The FEV_1/FVC ratio is <0.70.
- FEV_1 is decreased.
- TLC is increased.
- Residual volume is increased.

B. Clinical Features

1. Symptoms
   a. Any combination of cough, sputum production, and dyspnea (on exertion or at rest, depending on severity) may be present.
   b. Earliest symptom is exertional dyspnea, which may be difficult to detect in patients with sedentary lifestyles who avoid exertion.
2. Signs—the following may be present:
   a. Normal physical examination in early disease
   b. Prolonged expiratory time with pursed lip breathing
   c. During auscultation, end-expiratory wheezes on forced expiration, decreased breath sounds, crackles at the lung bases
   d. Hyperresonance on percussion and distant heart sounds
   e. Signs of cor pulmonale: hepatomegaly, distension of neck veins with expiration
   f. Signs of severe COPD:
      - Tachypnea
      - Tachycardia
      - Cyanosis
      - Use of accessory respiratory muscles
      - Positions that relieve dyspnea: tripod position (leaning forward with weight of arms on knees)

TABLE 2-1 COPD—Emphysema and Chronic Bronchitis

Predominant Emphysema ("Pink Puffers")	Predominant Chronic Bronchitis ("Blue Bloaters")
• Patients tend to be thin due to increased energy expenditure during breathing. • When sitting, patients tend to lean forward. • Patients have a barrel chest (increased AP diameter of chest).	• Patients tend to be overweight and cyanotic (secondary to chronic hypercapnia and hypoxemia). • Chronic cough and sputum production are characteristic. • Signs of cor pulmonale may be present in severe or long-standing disease.
Tachypnea with prolonged expiration through pursed lips is present.	Respiratory rate is normal or slightly increased.
Patient is distressed and uses accessory muscles (especially strap muscles in neck).	Patient is in no apparent distress, and there is no apparent use of accessory muscles.

Quick HIT

FEV_1 is the amount of air that can be forced out of the lungs in 1 second. The lower the FEV_1, the more difficulty one has breathing.

C. Diagnosis

1. PFT (spirometry)—see Table 2-2 and Figure 2-1
   a. This is the definitive diagnostic test
   b. Obstruction is evident based on the following:
      - Decreased FEV_1 (the forced expiratory volume in the first second of expiration)
        AND
      - FEV_1/FVC ratio <0.7 (FVC is the forced vital capacity, the maximal amount of air that can be forcibly exhaled after taking the deepest breath possible)
      - GOLD staging is based on FEV_1. FEV_1 ≥80% of predicted value is mild disease, 50% to 80% is moderate disease, 30% to 50% is severe disease, and <30% is very severe disease

- Disease severity is also clinically staged with GOLD “ABCD” groups based on number of exacerbations requiring hospitalization and degree of symptoms. This guides treatment options
- Increased total lung capacity (TLC), residual volume, and functional reserve capacity (FRC) (indicating air trapping) (see Figure 2-2). Although COPD increases TLC, the excess volume in the lung is not useful because it all becomes residual volume and does not participate in gas exchange
- Decreased vital capacity

CLINICAL PEARL 2-1

Key Points in Taking History of COPD Patients

General

- History of cardiopulmonary diseases
- Smoking history (duration, intensity, current smoker)
- Family history—COPD, heart disease, asthma
- Occupation—industrial dusts, fumes
- Overall health
- History of respiratory infections—frequency, severity
- History of hospitalizations for COPD or exacerbations
- Pulmonary medications

Pulmonary Symptoms

- Dyspnea—quantify severity
- Cough
- Sputum production—quantity, quality, duration, hemoptysis
- Wheezing

Adapted with permission from Burton GG, Hodgkin JE, Ward JJ, eds. *Respiratory Care—A Guide to Clinical Practice*. 4th ed. Lippincott Williams & Wilkins; 1997:1026. Table 28-3.

TABLE 2-2 Obstructive Versus Restrictive Lung Disease

Measurement	Obstructive	Restrictive
FEV_1	Low	Normal or slightly low
FEV_1/FVC	Low	Normal or high
Peak expiratory flow rate	Low	Normal
Residual volume	High	Low, normal, or high
Total lung capacity	High	Low
Vital capacity	Low	Low

Quick HIT

To diagnose airway obstruction, one must have a normal or increased TLC with a decreased FEV_1.

2. Chest radiograph (CXR)
   a. Low sensitivity for diagnosing COPD; only severe, advanced emphysema will show the typical changes, which include the following:
      - Hyperinflation, flattened diaphragm, enlarged retrosternal space (see Figure 2-3)
      - Diminished vascular markings
   b. Useful in an acute exacerbation to rule out complications such as pneumonia or pneumothorax
3. Measure α_1-antitrypsin levels in patients with a personal or family history of premature emphysema (≤45 years old) or emphysema in nonsmokers
4. Arterial blood gas (ABG) in those with SpO_2 <92% by pulse oximetry, depressed level of consciousness, or acute exacerbation—chronic $PaCO_2$ retention, decreased PaO_2, respiratory acidosis with or without appropriate metabolic compensation

Quick HIT

COPD leads to chronic respiratory acidosis with metabolic alkalosis as compensation.

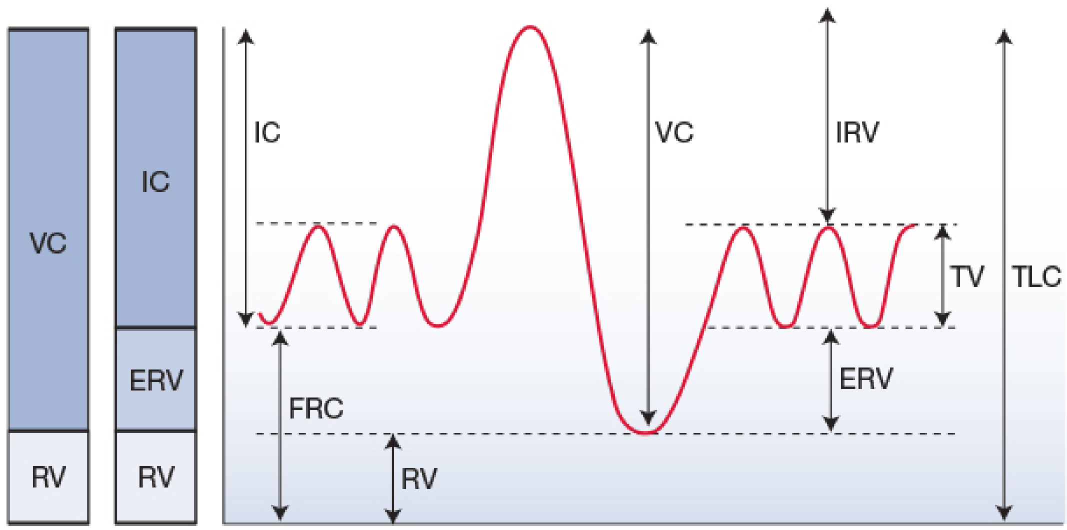


FIGURE 2-1 **Lung volumes. IC, inspiratory capacity; ERV, expiratory reserve volume.**

	$FEF_{50\%}$
Normal	3.2
Obstruction	0.5
Restriction	1.9

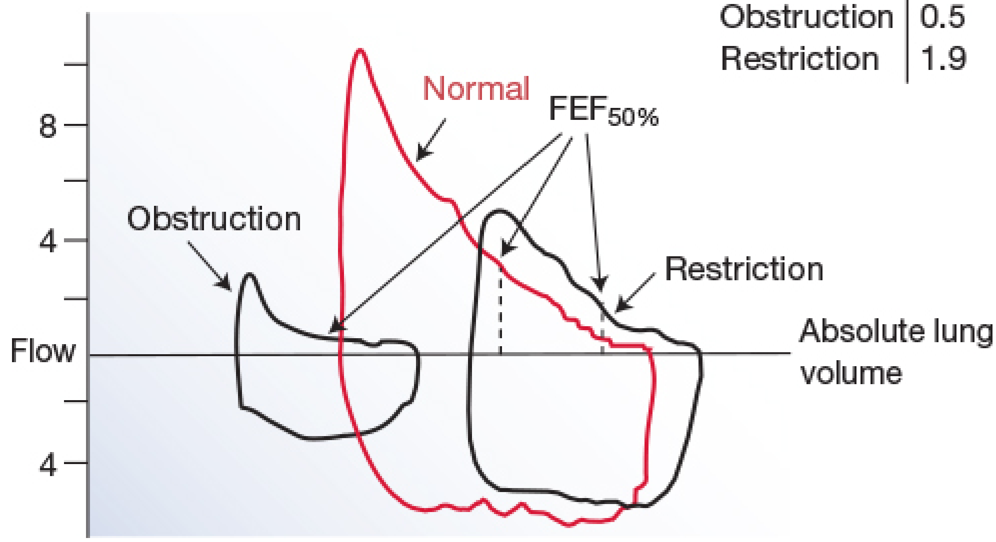


FIGURE 2-2 **Flow volume loops. Examples of flow volume curves in a patient with obstructive disease and a patient with restriction (diffuse interstitial fibrosis), as compared with a healthy person. Volumes on the axis are absolute volumes to better show the relation of flows (e.g., $FEF_{50\%}$) to hyperinflation and restriction.**
(Redrawn with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:2580. Figure 387.2.)

A 42-year-old woman presents with progressive fatigue over the past few weeks. She reports muscle fatigue, occasional double vision, and some difficulty breathing. She has no relevant past medical history and takes no medications. On examination, sustained upward gaze leads to muscle fatigue and bilateral ptosis. Pulmonary function testing is performed and is shown below.

FEV_1	85% of predicted
Forced vital capacity (FVC)	85% of predicted
FEV_1/FVC	105% of predicted
Total lung capacity (TLC)	70% of predicted
Diffusion capacity of the lung for carbon monoxide (DLCO)	100% of predicted

Which of the following is responsible for this patient's pattern on pulmonary function testing?

A. Chronic obstructive pulmonary disease
B. Neuromuscular disease
C. Pulmonary fibrosis
D. Pulmonary hemorrhage

- **The answer is B: Neuromuscular disease.** Myasthenia gravis is a neuromuscular disease caused by autoantibodies directed against postsynaptic acetylcholine receptors. Neuromuscular diseases can show a restrictive pattern (decreased FEV_1 and FVC but normal/increased FEV_1/FVC ratio) on pulmonary function testing that is extrinsic to the lung itself and therefore will have a normal DLCO. Examples include lower motor neuron disease (e.g., Guillain–Barré syndrome), myasthenia gravis, Lambert–Eaton

syndrome, muscular dystrophies, chest wall deformities (e.g., scoliosis and pectus carinatum), and obesity. **(A)** COPD will present with an obstructive pattern on spirometry (decreased FEV_1/FVC ratio) with a decreased DLCO (if there is a prominent component of emphysema). **(C)** Pulmonary fibrosis is a type of interstitial lung disease, which will show a restrictive pattern on spirometry as well as a decreased DLCO from parenchymal destruction and scarring. **(D)** Pulmonary hemorrhage would present with normal spirometry but an *increased* DLCO, since the presence of red blood cells within the airways will cause a rapid consumption of carbon monoxide during the test.

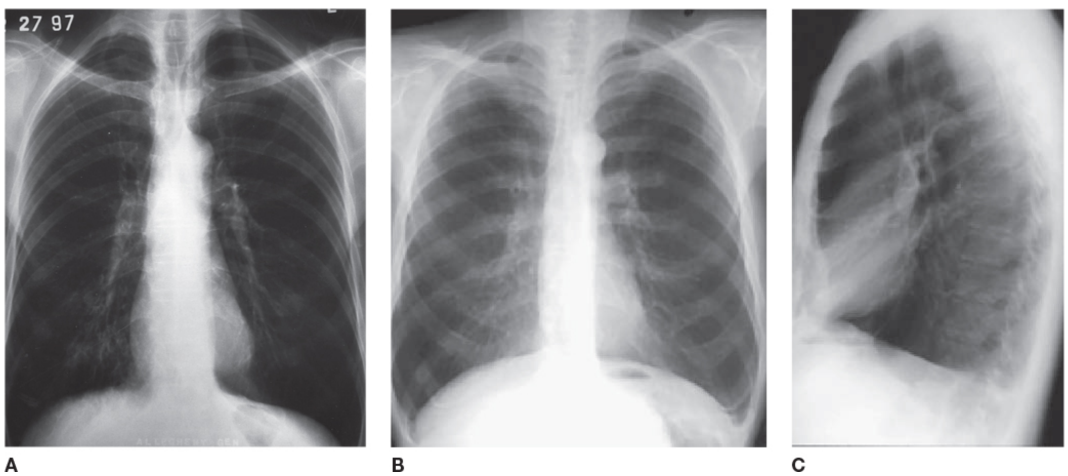


FIGURE 2-3 **Chest radiographs showing a patient with COPD.** (**A** reprinted with permission from Daffner RH. *Clinical Radiology: The Essentials.* 3rd ed.: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2007:136. Figure 4.87A. **B** and **C** reprinted with permission from Stern EJ, White CS. *Chest Radiology Companion*. Lippincott Williams & Wilkins; 1999:189. Figure 13-1A,B.)

D. Treatment

1. Modalities

   a. **Smoking cessation—the most important intervention**

   - Disease progression is accelerated by continued smoking and can be greatly slowed by its cessation.

- At around age 35, FEV_1 decreases approximately 25 to 30 mL/yr. In smokers, the rate of decline is faster (three- to fourfold). If a smoker quits, the ***rate of decline*** of FEV_1 slows to that of someone of the same age who has never smoked. **However,quitting does *not* result in complete reversal.**
- **Smoking cessation prolongs the survival rate but does not reduce it to the level of someone who has never smoked** (see Figure 2-4).
- Respiratory symptoms improve within 1 year of quitting.

b. Inhaled antimuscarinic bronchodilators
- Slower onset of action than the β-agonists, but last longer
- Short-acting muscarinic antagonists (SAMA): for example, ipratropium
- Long-acting muscarinic antagonists (LAMA) for patients with more severe symptoms: for example, tiotropium

c. Inhaled β_2-agonists (e.g., albuterol): bronchodilators
- Provide symptomatic relief
- Short-acting β_2-agonists (SABA, e.g., albuterol)
- Long-acting β-agonists (LABA) for patients requiring frequent use (e.g., salmeterol)

d. Combination of SABA with SAMA (SABA + SAMA, e.g., albuterol + ipratropium)
- More efficacious than either agent alone in bronchodilation
- Also helps with adherence to therapy (both medications in one inhaler)
- Other combinations exist (e.g., LAMA + LABA such as tiotropium-olodaterol) and may improve adherence

e. Inhaled corticosteroids (e.g., budesonide, fluticasone, mometasone): anti-inflammatory
- May minimally slow down the decrease in FEV_1 over time; however, many studies have failed to show any benefit in pulmonary function. May also increase rates of pulmonary infection
- Typically used in combination with a long-acting bronchodilator for patients with significant symptoms or repeated exacerbations
- Most useful in patients with serum eosinophils >300 cells/μL

f. Theophylline (oral)—role is controversial
- May improve mucociliary clearance and central respiratory drive.
- Narrow therapeutic index, so serum levels must be monitored.
- More side effects than other bronchodilators. Occasionally used for patients with refractory COPD.

g. Phosphodiesterase-4 inhibitors (e.g., roflumilast)
- Promote smooth muscle relaxation and decrease inflammation.
- May reduce risk of frequent exacerbations.

h. Oxygen therapy
- **Shown to improve survival and quality of life in patients with COPD *and* chronic hypoxemia.**
- Some patients need continuous oxygen, whereas others only require it during exertion or sleep. Get an ABG to determine need for oxygen (see Quick Hit).
- Long-standing hypoxemia may lead to pulmonary hypertension (HTN) and ultimately cor pulmonale. Continuous oxygen therapy for ≥18 hrs/day has been shown to reduce mortality in patients with these complications by controlling pulmonary HTN.

i. Pulmonary rehabilitation—education, exercise, physiotherapy: A major goal is to improve exercise tolerance. Pulmonary rehabilitation improves functional status and quality of life, and may reduce mortality after hospital discharge

j. Vaccination
- Influenza vaccination annually for all patients.
- Vaccination against *Streptococcus pneumoniae*—should be offered to all adult patients with COPD, regardless of age. Offer once before age 65, then once over age 65.

k. Antibiotics are given for acute exacerbations (see below)—increased sputum production in volume or change in character or worsening shortness of breath (SOB)

l. Surgery—may be beneficial in selected patients; carefully weigh potential benefits with risks. Options include the following:
- Lung volume resection surgery
- Lung transplantation

Quick HIT

Clinical monitoring of COPD patients entails the following:

- Serial FEV_1 measurements—this has the highest predictive value
- Pulse oximetry
- Severity of symptoms: exercise tolerance, cough, sputum, breathlessness

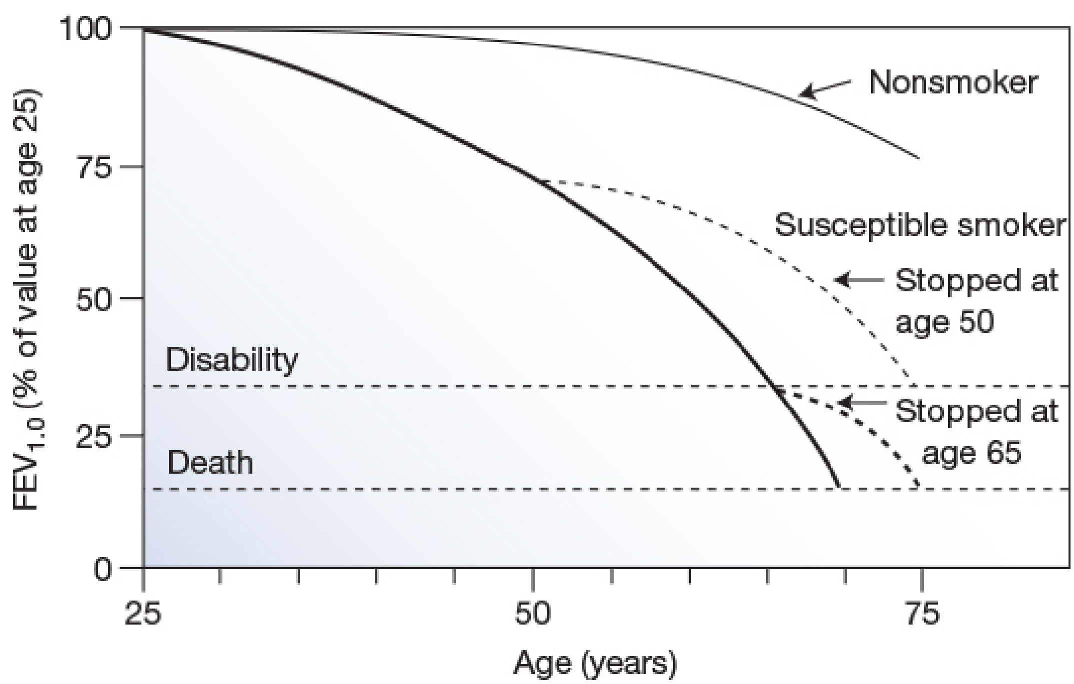


FIGURE 2-4 Smoking and COPD. Age-related rate of decline in lung function ($FEV_{1.0}$) in a nonsmoker (top) and susceptible smoker (bottom). The *dashed lines* indicate the beneficial effects of smoking cessation with moderate and severe disease. The accelerated decline in lung function approaches the normal rate, significantly delaying the onset of disability and death.

(Redrawn from Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J*. 1977;1(6077):1645–1648 with permission from BMJ Publishing Group Ltd.)

Quick HIT

Smoking cessation and home oxygen therapy are the only interventions shown to consistently lower mortality.

Quick HIT

- Treat COPD with bronchodilators (antimuscarinics, β_2-agonists, or both).
- Give steroids and antibiotics for acute exacerbations.

Quick HIT

If persistent COPD symptoms, review medication adherence and inhaler technique.

Quick HIT

Systemic glucocorticoids are only used for acute exacerbations and should not be used for long-term treatment, even for patients with severe COPD.

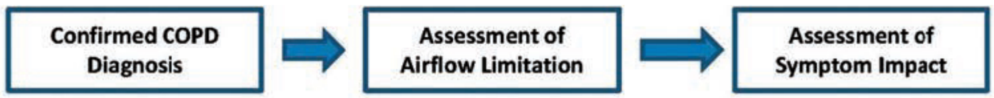
Quick HIT

Criteria for continuous or intermittent long-term oxygen therapy in COPD:

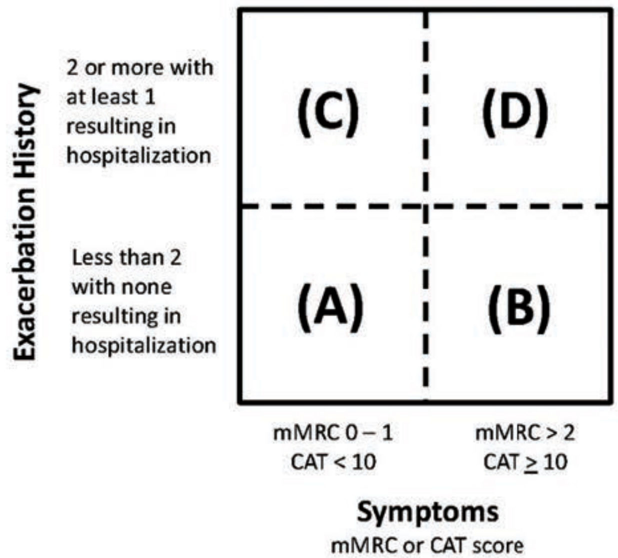
- PaO_2 **55 mm Hg** *OR*
- **O_2 saturation ≤88%** (pulse oximetry), either at rest or during exercise *OR*
- PaO_2 55 to 59 mm Hg plus polycythemia or evidence of cor pulmonale
- Note that the above must be consistent findings despite optimal medical therapy

2. Treatment guidelines—stepwise therapy based on severity of symptoms and prior number of exacerbations or COPD-related hospitalizations (see Figure 2-5)
   a. Low risk of exacerbation (0 to 1 exacerbations in past year)
      - Begin with a short-acting bronchodilator (antimuscarinic and/or β-agonist) as needed in a metered-dose inhaler (MDI) formulation (with spacer to improve delivery).
      - Add daily long-acting bronchodilator, if more symptomatic.
   b. High risk of exacerbation (2 or more exacerbations per year)
      - Regular use of long-acting bronchodilator (antimuscarinic and/or β-agonist)

- Add inhaled corticosteroid, if more symptomatic
- Consider additional agents (roflumilast or theophylline)
- Continuous oxygen therapy (if patient is hypoxemic)
- Pulmonary rehabilitation



	FEV_1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50–79
GOLD 3	30–49
GOLD 4	< 30



Interpretation:	
Patient Group (A): Low risk, fewer symptoms	Mild to moderate impact of symptoms on daily living; GOLD 1 or 2 likely; single bronchodilator therapy management recommended.
Patient Group (B): Low risk, more symptoms	Moderate or greater impact of symptoms on daily living; GOLD 1 or 2 likely; one or more long-acting β_2 agonist (LABA) or antimuscarinic (LAMA) bronchodilators for management recommended; explore possible comorbidities contributing to symptoms; initiate pulmonary rehab & breathlessness self-management.
Patient Group (C): High risk, fewer symptoms	Mild to moderate impact of symptoms on daily living with at least one exacerbation requiring hospitalization; recommend LAMA and adding LABA/LAMA or inhaled corticosteroid (IHC) if necessary; initiate pulmonary rehab and breathlessness self-management.
Patient Group (D): High risk, more symptoms	Moderate to severe impact of symptoms on daily living; combination LABA/LAMA recommended; high risk of pneumonia cited with IHC use; add anti-inflammatory (rofluilast) and/or macrolide antibiotic (i.e., azithromycin) for exacerbation prevention; discuss palliative and advanced care strategies.

FIGURE 2-5 Treatment guidelines for chronic obstructive lung disease, based on the revised 2017 Global Initiative for Obstructive Lung Disease (GOLD) guidelines.
(Reprinted with permission from Thompson WR. *ACSM's Clinical Exercise Physiology*. Wolters Kluwer; 2019. Figure 9.9.)

3. Acute COPD exacerbation. Definition: Increased dyspnea, sputum production, and/or cough. Acute COPD exacerbation can lead to acute

respiratory failure requiring hospitalization, and possibly mechanical ventilation; potentially fatal

a. Bronchodilators (β_2-agonist) alone or in combination with antimuscarinics are first-line therapy.
b. Systemic corticosteroids are used for patients requiring hospitalization. A short course of oral prednisone is common practice.
c. Antibiotics (azithromycin, doxycycline, or fluoroquinolones): Reserved for those with moderate or severe exacerbations requiring hospitalization. Beware of common adverse effects (e.g., QT prolongation with azithromycin, fluoroquinolones).
d. Supplemental oxygen is used to keep O_2 saturation 88% to 92%. Start with a nasal cannula; a face mask may need to be used.
    - If SaO_2 is >92%, the patient is at risk of CO_2 retention from worsening ventilation/perfusion (V/Q) mismatch and the Haldane effect (not from loss of hypoxic respiratory drive).
e. Noninvasive positive pressure ventilation (NPPV) (bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP]): Studies have shown a benefit in acute exacerbations. It may decrease the likelihood of respiratory failure requiring invasive mechanical ventilation.
f. Intubation and mechanical ventilation may be required if the above do not stabilize the patient. Intubate, if increasing respiratory rate (RR), increasing $PaCO_2$, and worsening acidosis.

Quick HIT

- One of the main treatment goals for COPD patients is to reduce the number and severity of exacerbations they experience each year.
- Pulmonary infection (most commonly viruses, followed by bacteria such as *S. pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Moraxella catarrhalis*) is one of the main precipitants of a COPD exacerbation.

Quick HIT

If a patient presents with COPD exacerbation, the following steps are appropriate:

- CXR
- β_2-Agonist and antimuscarinic inhalers
- Systemic corticosteroids
- Antibiotics
- Supplemental oxygen
- NPPV, if needed (see Clinical Pearl 2-9)

E. Complications

1. Acute exacerbations—most common causes are infection, nonadherence with therapy, and cardiac disease
2. Secondary polycythemia (Hct >55% in men or >47% in women)—compensatory response to chronic hypoxemia
3. Pulmonary HTN and cor pulmonale—may occur in patients with severe, long-standing COPD who have chronic hypoxemia

A 59-year-old woman with a history of hypertension and COPD presents to the hospital with shortness of breath with an increased cough and sputum production. She has a temperature of 37.6 °C, blood pressure of 138/88 mm Hg, heart rate of 96 beats/min, respiratory rate of 28 breaths/min, and oxygen saturation of 84% on room air. She is anxious and is using respiratory accessory muscles to breathe. There is hyperresonance to percussion along both lung fields with wheezes and rhonchi heard bilaterally. The CXR does not show any infiltrates.

Which of the following is NOT an appropriate first-line treatment for the patient at this time?

A. Oxygenation
B. Methylprednisolone
C. Azithromycin
D. Inhaled corticosteroids

- **The answer is D: Inhaled corticosteroids.** This patient is presenting with a history of COPD with an acute exacerbation, which is defined as an increase in any of the chronic symptoms of COPD (increased frequency/severity of cough, increased dyspnea, or increased sputum amount or change in color). The majority of acute exacerbations are caused by respiratory infections. **(A, B, C)** Management of acute COPD exacerbations should be differentiated from the management of chronic disease. Important therapies during an exacerbation include oxygen administration targeting an SaO_2 of 88% to 92%, inhaled bronchodilators (anticholinergics and β_2-agonists), systemic corticosteroids, and antibiotics. Antibiotics show some benefit in COPD exacerbations. **(D)** Although inhaled corticosteroids are useful in the chronic treatment of COPD, there is no evidence for their use in acute exacerbations and should not be used instead of systemic corticosteroids.

Asthma

A. General Characteristics

1. Characteristically defined by the following triad:
   a. Airway inflammation
   b. Airway hyperresponsiveness
   c. Reversible airflow obstruction
2. **Asthma can begin at any age**
3. Extrinsic versus intrinsic asthma
   a. Extrinsic asthma (most cases)
      - Patients are atopic, that is, produce immunoglobulin E (IgE) to environmental antigens. May be associated with eczema and hay fever.
      - Patients become asthmatic at a young age.
   b. Intrinsic asthma—not related to atopy or environmental triggers
4. Triggers include aeroallergens (pollens, house dust, molds, cockroaches, animals), irritants (tobacco smoke, cannabis, woodburning, fumes), cold air, exercise, viral infections, and medications (β-blockers, aspirin, certain eye drops)

CLINICAL PEARL 2-2

"All That Wheezes Is Not Asthma"

The most common cause of wheezing is asthma. However, any condition that mimics large airway bronchospasm can cause wheezing.

- CHF—due to edema of airways and congestion of bronchial mucosa
- COPD—inflamed airways may be narrowed, or bronchospasm may be present
- Cardiomyopathies, pericardial diseases can lead to edema around the bronchi
- Lung cancer—due to obstruction of airways (central tumor or mediastinal invasion)

Quick HIT

Signs of acute severe asthma attacks:

- Tachypnea, diaphoresis, wheezing, speaking in incomplete sentences, and use of accessory muscles of respiration.
- Paradoxic movement of the abdomen and diaphragm on inspiration is sign of impending respiratory failure.

B. Clinical Features

1. Characterized by intermittent symptoms that include **SOB, wheezing, chest tightness,** and **cough.** Symptoms have variable severity and may not be present simultaneously. Usually occur within 30 minutes of exposure to triggers.
2. Symptoms are typically worse at night.
3. Wheezing (commonly during expiration, but can occur during inspiration) is the most common finding on physical examination (see Clinical Pearl 2-2).

C. Diagnosis

1. Pulmonary function tests (PFTs) are required for diagnosis. They show an obstructive pattern: decrease in expiratory flow rates, decreased FEV_1, and decreased FEV_1/FVC ratio (<0.70). Note that PFTs may be normal if asymptomatic at the time. These patients may require repeat testing during symptoms or bronchoprovocation testing.
2. Spirometry before and after bronchodilators can confirm diagnosis by proving reversible airway obstruction. If inhalation of a bronchodilator (β_2-agonist) results in an increase in FEV_1 or FVC by at least 12%, airflow obstruction is considered reversible.
3. Peak flow (peak expiratory flow rate)—useful measure of airflow obstruction, but can be limited by patient effort and technique. Patients should self-monitor their peak flow:
   a. Mild persistent asthma: Periodic monitoring is sufficient. Increase the dose of inhaled steroid, if the peak flow decreases.
   b. Moderate persistent asthma: Daily monitoring is required. Increase the dose of inhaled steroid, if the peak flow decreases.

c. Severe persistent asthma: Daily monitoring is required. Initiate prednisone, if the peak flow decreases.

4. Bronchoprovocation test
   a. Useful when asthma is suspected but PFTs are nondiagnostic.
   b. Measures ease with which airways narrow in response to stimuli (hyperresponsiveness).
   c. Measures lung function before and after inhalation of increasing doses of methacholine (muscarinic agonist); hyperresponsive airways develop obstruction at lower doses.
5. CXR
   a. Normal in mild to moderate cases; severe asthma may show hyperinflation.
   b. Only necessary in severe asthma to exclude other conditions (e.g., pneumonia, pneumothorax, pneumomediastinum, foreign body).
6. ABGs
   a. ABGs should be considered if the patient is in significant respiratory distress. **Hypocarbia** is common. Hypoxemia may be present.
   b. If the $PaCO_2$ is normal or increased, respiratory failure may ensue.
      - Remember that patients with an asthma attack have an increased RR, which should cause the $PaCO_2$ to decrease. Increasing $PaCO_2$ is a sign of respiratory muscle fatigue or severe airway obstruction.
      - The patient should be hospitalized and mechanical ventilation considered.

Quick HIT

PFTs in asthma:
1. Decreased FEV_1, decreased FVC, decreased FEV_1/FVC ratio
2. Increase in FEV_1 >12% with albuterol
3. Decrease in FEV_1 >20% with methacholine or histamine

Quick HIT

Although asthma can be diagnosed with PFTs and spirometry, in an acute setting (ED) when patient is SOB, history and observed response to antiasthma medication is quickest method of diagnosis.

TABLE 2-3 Chronic Treatment of Asthma

Severity	Initial Therapy
Mild intermittent (symptoms two or fewer times per week)	SABA as needed Low-dose ICS as needed
Mild persistent (symptoms two or more times per week but not every day)	Low-dose ICS daily Low-dose ICS + LABA combination inhaler as needed
Moderate persistent (daily symptoms; frequent exacerbations)	Low-dose ICS + LABA combination inhaler daily
Severe persistent (continual symptoms, frequent exacerbations, limited physical activity)	Medium-dose ICS + LABA combination inhaler daily Consider add-on therapies like tiotropium, biologics like omalizumab (anti-IgE), systemic corticosteroids, others

Note: All patients should have intermittent short-acting inhaled β_2-agonists as needed plus long-term control medications based on the severity of their asthma.

ICS, inhaled corticosteroid; SABA, short-acting β-agonist; LABA, long-acting β-agonist.

From The National Asthma Education and Prevention Program, Expert Panel Report III: 2007.

Quick HIT

During asthma exacerbations, the patient hyperventilates, leading to low $PaCO_2$ levels. If the patient is no longer hyperventilating (CO_2 level is normal or high), this could be a sign that the patient is decompensating (due to fatigue) and that intubation may be required.

Quick HIT

Avoid nonselective β-blockers in asthmatics!

D. Treatment

1. Available modalities (see Table 2-3)
   a. Inhaled β_2-agonists
      - Short-acting β_2-agonists (SABA, e.g., albuterol) are used for acute attacks (rescue). Onset is 2 to 5 minutes, duration is 4 to 6 hours.
      - Long-acting β_2-agonists (LABA, e.g., salmeterol) are often used in combination with inhaled corticosteroids for severe or persistent symptoms.
   b. Inhaled corticosteroids (ICS) for moderate to severe asthma
      - Preferred over oral steroids due to fewer systemic side effects. (Oral steroids are reserved for severe, persistent asthma.)
      - If used on a regular basis, airway hyperresponsiveness decreases, and the frequency of asthma exacerbations decreases.
   c. Montelukast—leukotriene modifiers—limited evidence but may be useful for prophylaxis of mild exercise-induced asthma and for control of moderate persistent disease. They may allow reductions in steroid and bronchodilator requirements
   d. Theophylline
      - Can be useful in addition to ICS for persistent symptoms.
2. Treatment of acute severe asthma exacerbation (hospital admission)
   a. Inhaled β_2-agonist (first-line therapy)
      - Via nebulizer or MDI (see Clinical Pearl 2-3)
      - Mainstays of emergency treatment—have an onset of action of minutes
      - Assess patient response to bronchodilators (clinically and with peak flows)
   b. Corticosteroids
      - Traditionally given intravenously initially, but may also be given orally if given in equivalent doses.

- Taper IV or oral corticosteroids, but only when clinical improvement is seen.
- Initiate inhaled corticosteroids at the beginning of the tapering schedule.

c. Third-line agent includes IV magnesium—not as effective as β-agonists; magnesium helps with bronchospasm but only used in acute severe exacerbation that has not responded to above medications (albuterol, steroids, oxygen).
d. Supplemental oxygen (keep oxygen saturation >90%).
e. Antibiotics, only if suspicion of bacterial pneumonia (as most triggers are viral).
f. Intubation for patients in respiratory failure or impending respiratory failure.
g. Guidelines for treatment are stepwise based on severity, which depends on frequency (intermittent vs. persistent) and symptom severity (mild, moderate, or severe). See Table 2-3.

CLINICAL PEARL 2-3

Metered-Dose Inhalers (MDIs) and Nebulizers

- An MDI with a spacer is just as effective as a nebulizer. A spacer is a holding chamber that obviates the need to coordinate inhalation and depression of the canister, and thus makes the use of an MDI easier. Its use leads to a greater bronchodilator effect because more of the drug is deposited in smaller airways and less accumulates in the oropharynx.
- A nebulizer is no more effective than an MDI, but patients may report greater relief of symptoms simply because it is more comfortable (patient does not have to coordinate breathing with medication administration). It may be preferred by patients with very severe asthma unresponsive to MDIs.

Quick HIT

- Side effects of inhaled corticosteroids are due to oropharyngeal deposition and include sore throat, oral candidiasis (thrush), and hoarseness.
- Using a spacer with MDIs and rinsing the mouth after use help minimize these side effects.

Quick HIT

For acute asthma exacerbation, test to order:
1. Peak expiratory flow—decreased
2. ABG—increased A–a gradient
3. CXR—rule out pneumonia, pneumothorax

Bronchiectasis

A. General Characteristics

1. There is permanent, abnormal dilation and destruction of bronchial walls with chronic inflammation, airway collapse, and ciliary loss/dysfunction leading to impaired clearance of secretions.
2. Less common today because modern antibiotics are used for respiratory infections.

Quick HIT

Complications of asthma:
1. Status asthmaticus—does not respond to standard medications
2. Acute respiratory failure (due to respiratory muscle fatigue)
3. Pneumothorax, atelectasis, pneumomediastinum

B. Causes

1. Recurrent infections (airway obstruction, immunodeficiency, allergic bronchopulmonary aspergillosis, mycobacterium)
2. Cystic fibrosis (CF) is the most common cause of bronchiectasis (accounts for half of all cases)
3. Primary ciliary dyskinesia (e.g., Kartagener syndrome)
4. Autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus, Crohn disease, etc.)
5. Humoral immunodeficiency (abnormal lung defense), airway obstruction

Quick HIT

- Aspirin-sensitive asthma should be considered in patients with asthma and nasal polyps.
- Avoid aspirin or any nonsteroidal anti-inflammatory drugs in these patients because they may cause a severe systemic reaction.

C. Clinical Features

1. Chronic cough with large amounts of mucopurulent, foul-smelling sputum
2. Dyspnea
3. Hemoptysis—due to rupture of blood vessels near bronchial wall surfaces; usually mild and self-limited, but sometimes can be brisk and presents as an emergency
4. Recurrent or persistent pneumonia

Quick HIT

A variety of infections can cause bronchiectasis by destroying and damaging the bronchial walls and interfering with ciliary action.

D. Diagnosis

1. High-resolution CT (HRCT) scan is the diagnostic study of choice, which will show airway dilatation.
2. PFTs reveal an obstructive pattern.
3. CXR is abnormal in most cases, but findings are nonspecific.
4. Bronchoscopy may be helpful for infectious workup.

E. Treatment

1. Antibiotics for acute exacerbations—superimposed infections are signaled by change in quality/quantity of sputum, fever, chest pain, etc. Selection of antibiotic is based on patient's prior sputum microbiology results. Check a sputum culture.
2. Bronchial hygiene is very important
   a. Hydration

b. Chest physiotherapy (postural drainage, chest percussion) to help remove the mucus
c. Inhaled bronchodilators

Quick HIT

The main goal in treating bronchiectasis is to prevent the complications of pneumonia and hemoptysis.

Cystic Fibrosis

- Autosomal recessive condition predominantly affecting Caucasians.
- Defect in chloride channel protein causes impaired chloride and water transport, which leads to excessively thick, viscous secretions in the respiratory tract, exocrine pancreas, sweat glands, intestines, and genitourinary tract.
- Typically results in obstructive lung disease pattern with chronic pulmonary infections (frequently *Pseudomonas*), pancreatic insufficiency, and other GI complications.
- Treatment is pancreatic enzyme replacement, fat-soluble vitamin supplements, chest physical therapy, vaccinations (influenza and pneumococcal), treatment of infections with antibiotics, inhaled recombinant human deoxyribonuclease (DNase), which breaks down the DNA in respiratory mucus that clogs the airways.
- Traditionally considered a pediatric topic; however, the prognosis has improved significantly, with the median age of death now over 30 years of age.

Lung Neoplasms

Lung Cancer

A. General Characteristics

1. Pathologic types are divided into two subgroups:

a. Small cell lung cancer (SCLC)—15% of lung cancers
b. Non–small cell lung cancer (NSCLC)—85% of lung cancers; includes squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and bronchoalveolar cell carcinoma

2. Risk factors
   a. Cigarette smoking—accounts for >85% of cases
      - There is a linear relationship between pack-years of smoking and risk of lung cancer.
      - Adenocarcinoma has the **lowest** association with smoking of all lung cancers.
   b. Second-hand smoke
   c. Asbestos
      - Common in shipbuilding and construction industry, car mechanics, painting.
      - Smoking and asbestos in combination synergistically increase the risk of lung cancer.
   d. Radon—high levels found in basements
   e. COPD—an independent risk factor after smoking is taken into account
3. Staging
   a. NSCLC is staged via the primary TNM system (this stands for Tumor, Nodes, Metastasis, and is a commonly used classification system for cancer)
   b. SCLC is staged differently (though some recommend TNM staging still be used):
      - Limited—confined to chest plus supraclavicular nodes, but not cervical or axillary nodes
      - Extensive—outside of chest and supraclavicular nodes

***Quick* HIT**

In the diagnosis of lung cancer, it is crucial to differentiate between small cell (15%) and non–small cell (85%) types because the treatment approach is completely different (see below). A tissue diagnosis is necessary to make this differentiation.

Quick HIT

Unfortunately, signs and symptoms are generally nonspecific for lung cancer, and by the time they are present, disease is usually widespread.

B. Clinical Features

1. Local manifestations (squamous cell carcinoma is most commonly associated with these symptoms)
   a. Airway involvement can lead to cough, hemoptysis, obstruction, wheezing, dyspnea
   b. Recurrent pneumonia (postobstructive pneumonia)
2. Constitutional symptoms
   a. Anorexia, weight loss, weakness
   b. Usually indicative of advanced disease
3. Local invasion
   a. **Superior vena cava (SVC) syndrome**—occurs in 5% of patients
      - Caused by obstruction of SVC by a mediastinal tumor
      - More commonly associated with SCLC (but also occurs with NSCLC)
      - Findings: facial fullness; facial and arm edema; dilated veins over anterior chest, arms, and face; jugular venous distention (JVD)
   b. Phrenic nerve palsy—occurs in 1% of patients
      - Destruction of phrenic nerve by tumor; phrenic nerve courses through the mediastinum to innervate the diaphragm
      - Results in hemidiaphragmatic paralysis
   c. Recurrent laryngeal nerve palsy (3% of patients)—causes hoarseness
   d. **Horner syndrome**—due to invasion of cervical sympathetic chain by an apical tumor. Symptoms: unilateral facial anhidrosis (no sweating), ptosis, and miosis
   e. **Pancoast tumor**
      - Superior sulcus tumor—an apical tumor involving C8 and T1 to T2 nerve roots, causing shoulder pain radiating down the arm
      - Usually NSCLC. In past, mainly squamous cell carcinomas, now more commonly adenocarcinomas

- Symptoms: pain; upper extremity weakness due to brachial plexus invasion; associated with Horner syndrome 60% of the time

f. Malignant pleural effusion—occurs in 10% to 15% of patients

- Prognosis is very poor—equivalent to distant metastases

4. Metastatic disease—most common sites are brain, bone, adrenal glands, and liver
5. Paraneoplastic syndromes

a. Syndrome of inappropriate ADH: usually associated with small cell carcinoma (10% of SCLC patients)

b. Cushing syndrome: due to ectopic ACTH secretion, typically associated with small cell carcinoma

c. Hypercalcemia: commonly due to PTH-like hormone secretion, most commonly squamous cell carcinoma

d. Hypertrophic pulmonary osteoarthropathy: associated with both adenocarcinoma and squamous cell carcinoma; severe long-bone pain may be present, and leads to digital clubbing

e. **Eaton–Lambert syndrome:** most common in SCLC; clinical picture is similar to that of myasthenia gravis, with proximal muscle weakness/fatigability, diminished deep tendon reflexes, paresthesias (more common in lower extremities)

***Quick* HIT**

Prognosis of SCLC: For limited disease, 5-year survival is 10% to 13% (median survival ranges from 15 to 20 months). For extensive disease, 5-year survival rate is 1% to 2% (median survival is 8 to 13 months).

***Quick* HIT**

For lung cancer, obtain a CXR, a CT scan, and a tissue biopsy to confirm diagnosis and determine histologic type (SCLC or NSCLC).

C. Diagnosis

1. CXR

   a. Most important radiologic study for diagnosis, but **not** used as a screening test
   b. Demonstrates abnormal findings in nearly all patients with lung cancer
   c. Stability of an abnormality over a 2-year period is almost always associated with a benign lesion
2. CT scan of the chest with IV contrast
   a. Very useful for staging
   b. Can demonstrate extent of local and distant metastasis
   c. Very accurate in revealing lymphadenopathy in mediastinum
   d. Consider CT of abdomen to screen for metastases to adrenal glands and liver
3. Bronchoscopy with endobronchial ultrasound and transbronchial needle aspiration (EBUS-TBNA)
   a. First-choice diagnostic and staging procedure
   b. Best for central lesions and lymph nodes in paratracheal, subcarinal, and hilar regions of mediastinum
4. Whole-body positron emission tomography (PET)—provides additional information that primary tumor is malignant, detects lymph node and intrathoracic and distant metastases
5. Transthoracic needle biopsy (under fluoroscopic or CT guidance)
   a. Needle biopsy of suspicious pulmonary masses is highly accurate
   b. Invasive and must be used **only** in selected patients due to higher rates of pneumothorax. This is a better biopsy method for peripheral lesions, whereas central, peribronchial lesions should be biopsied using bronchoscopy
6. Mediastinoscopy
   a. Allows direct visualization of the superior mediastinum
   b. Identifies patients with advanced disease who would not benefit from surgical resection
7. Cytologic examination of sputum
   a. Noninvasive diagnostic tool for patients who wish to avoid biopsy or other more definitive testing
   b. Provides highly variable results with low yield; if negative and clinical suspicion is high, further tests are indicated

Quick HIT

- CXR may show pleural effusion, which should be tapped; the fluid should be examined for malignant cells.
- Regardless of the findings on CXR or CT scan, pathologic confirmation is required for definitive diagnosis of lung cancer.

Quick HIT

Always perform a biopsy for intrathoracic lymphadenopathy (specificity for metastasis is 60%).

D. Treatment

1. NSCLC
   a. Surgery is the best option for limited disease.
      - A definitive pathologic diagnosis must be made prior to surgery.
      - Patients with metastatic disease outside the chest are **not** candidates for surgery.
      - Recurrence may occur even after complete resection.

   b. Radiation therapy is an important adjunct to surgery.
   c. Chemotherapy is of uncertain benefit. Some studies show a modest increase in survival, especially with novel immunotherapy agents like PD-1 and PD-L1 blockers.
2. SCLC
   a. Often extensive at time of presentation.
   b. Very responsive to chemotherapy, so systemic chemotherapy is mainstay of treatment.
   c. For limited disease, combination of chemotherapy and radiation therapy is used initially.
   d. For extensive disease, chemotherapy is used alone as initial treatment. If patient responds to initial chemotherapy treatment, prophylactic whole-brain irradiation decreases incidence of brain metastases and prolongs survival.
   e. Surgery has a limited role because these tumors are usually nonresectable.

Quick HIT

The prognosis for lung cancer is grim. **Overall 5-year survival for lung cancer patients is 14%;** 85% of patients with SCLC have extensive disease at the time of presentation, and of these, almost all die within 2 years.

Quick HIT

Most asymptomatic masses are benign.

Solitary Pulmonary Nodule

A. A single, well-circumscribed nodule usually discovered incidentally with no associated mediastinal or hilar lymph node involvement. The main

question is whether the lesion is malignant and requires biopsy or resection (see Figure 2-6).

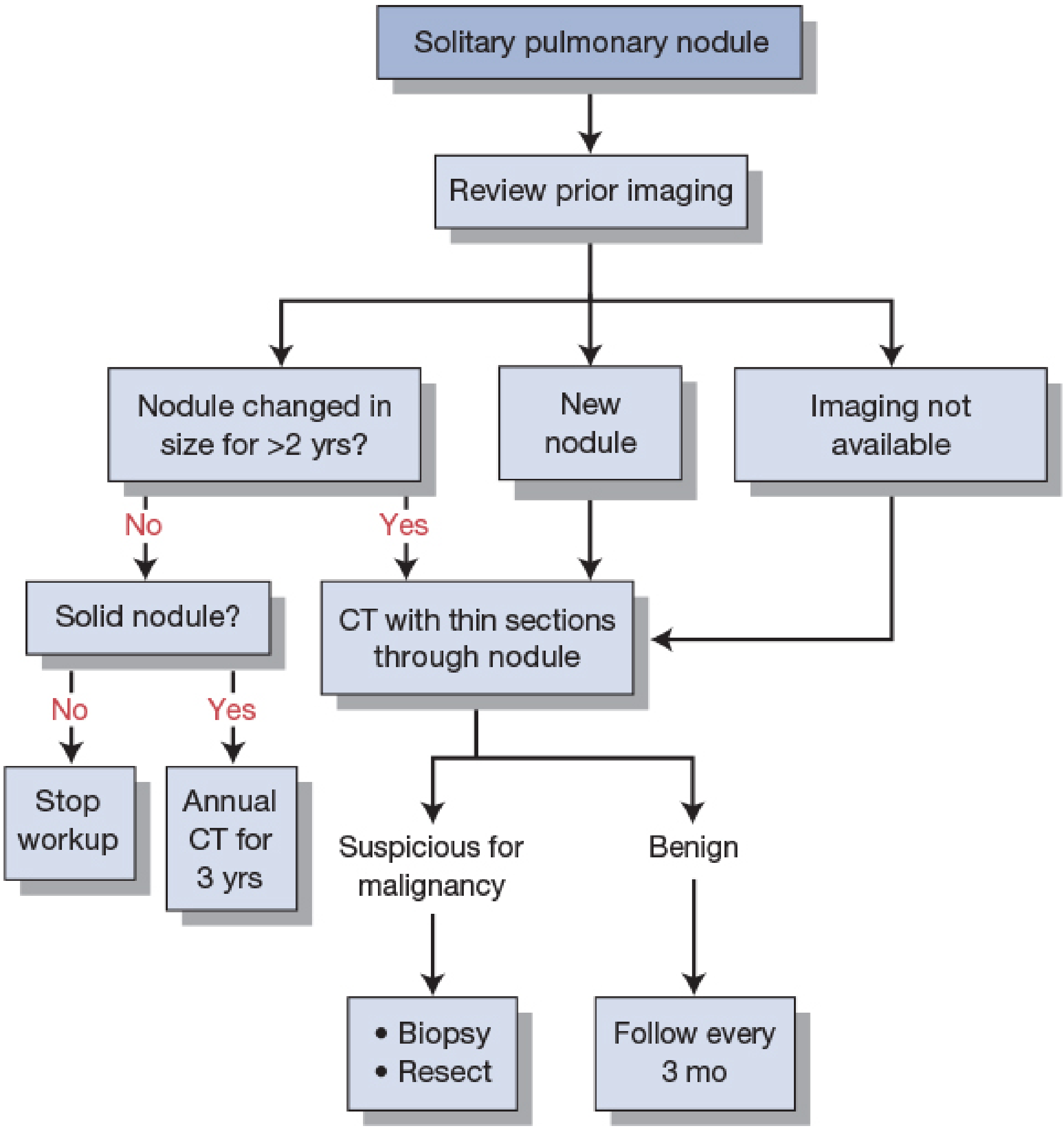


FIGURE 2-6 **Evaluation of a solitary pulmonary nodule.** (Adapted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:2574. Figure 386.6.)

TABLE 2-4 Types of Lung Cancer

Pathologic Type		Incidence	Location	Special Features
NSCLC	Squamous cell carcinoma	30% of all lung cancers	Usually central	Cavitation on CXR
	Adenocarcinoma	40% of all lung cancers—most common type	Often peripheral	• Pleural involvement in 20% of cases. • Less closely associated with smoking than other types. • Can be associated with pulmonary scars/fibrosis.
	Large cell carcinoma	15% of all lung cancers	Usually peripheral	
SCLC		15% of all lung cancers	Central	• Tend to narrow bronchi by extrinsic compression. • Widespread metastases are common. 50–75% of patients have metastases outside the chest at the time of presentation.

B. Has a wide differential diagnosis (e.g., infectious granuloma, bronchogenic carcinoma, hamartoma, bronchial adenoma), but one must investigate the possibility of malignancy because resection can lead to a cure with early detection.

C. Several features favor benign versus malignant nodules:

1. Age—the older the patient, the more likely it is malignant—over 50% chance of malignancy if patient age is over 60.
2. Smoking—if history of smoking, more likely to be malignant.
3. Size of nodule—the larger the nodule, the more likely it is malignant. Small is <8 mm, large >10 mm (>50% chance of malignancy).
4. Borders—malignant nodules have more irregular borders. Benign lesions have smooth/discrete borders.
5. Attenuation—solid nodules are more likely benign, subsolid (e.g., ground-glass) nodules have higher chance of malignancy but more difficult to biopsy.

6. Calcification—eccentric asymmetric calcification suggests malignancy. Dense, central calcification suggests benign lesion.
7. Growth—enlarging nodule suggests malignancy.

D. Considering the above factors, one designates the nodule as low, intermediate, or high probability of being malignant.

1. Low-probability nodules—serial CT scan
2. Intermediate-probability nodule, 1 cm or larger—PET scan. If PET positive, biopsy
3. High-probability nodule—biopsy (transbronchial, transthoracic, or video-assisted thoracoscopic surgery) followed by lobectomy, if appropriate

E. Previous imaging is very helpful: Every effort should be made to find a previous CXR or CT for comparison. If the lesion is stable for more than 2 years, it is likely benign. Malignant lesions grow relatively rapidly (growth is usually evident within months) (see Table 2-4). However, growth over a period of days is usually nonmalignant (often infectious/inflammatory) (see Table 2-5).

Mediastinal Masses

A. Causes

1. Metastatic cancer (especially from lung cancer)—most common cause of mediastinal mass in older patients
2. Most common cause according to location:
   a. Anterior mediastinum: “Four Ts”—thyroid, teratogenic tumors, thymoma, terrible lymphoma
   b. Middle mediastinum: lymphadenopathy (from lung cancer, lymphoma, sarcoidosis, etc.), aneurysms, cysts, Morgagni hernia, esophageal masses
   c. Posterior mediastinum: neurogenic tumors, enteric cysts, aneurysms, Bochdalek hernia

TABLE 2-5 Benign Versus Malignant Solitary Pulmonary Nodules

Factors That Favor a Benign Diagnosis	Factors That Favor Malignancy
Age <50 yrs	Age >50 yrs
Nonsmoker	Smoker or previous smoker
Size of nodule <5 mm	Size of nodule >10 mm
No growth over 2-yr period	Steady growth over serial imaging
Nodule circular and regular shaped	Nodule grossly irregular or with speculated margin
Central, laminated, or popcorn calcification	Stippled or eccentric pattern of calcification
Solid nodule	Subsolid nodule (e.g., ground-glass)

B. Clinical Features

1. Usually asymptomatic
   a. When symptoms are present, they are due to compression or invasion of adjacent structures
   b. Cough (compression of trachea or bronchi), sometimes hemoptysis
   c. Chest pain, dyspnea
   d. Postobstructive pneumonia
   e. Dysphagia (compression of esophagus)
   f. SVC syndrome
   g. Compression of nerves
      - Hoarseness (recurrent laryngeal nerve)
      - Horner syndrome (sympathetic ganglia)
      - Diaphragm paralysis (phrenic nerve)

Quick HIT

If CT scan suggests a benign mass and the patient is asymptomatic, observation is appropriate.

C. Diagnosis

1. Chest CT with IV contrast is test of choice
2. Usually discovered incidentally on a CXR performed for another reason

Diseases of the Pleura

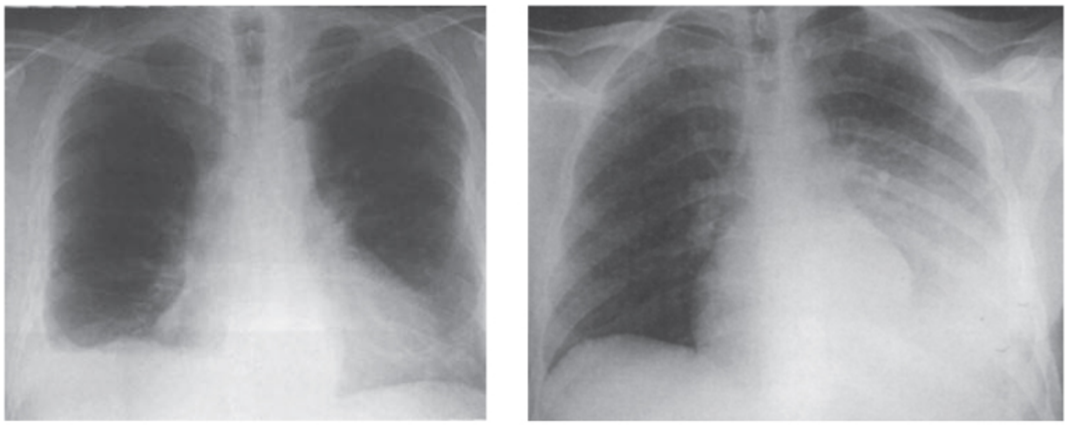
Pleural Effusion

A. General Characteristics

1. Caused by one of the following mechanisms: increased drainage of fluid into pleural space, increased production of fluid by cells in the pleural space, or decreased drainage of fluid from the pleural space (see Figure 2-7)
2. Transudative effusions—pathophysiology is due to either elevated capillary pressure in visceral or parenteral pleura (e.g., congestive heart failure [CHF]), or decreased plasma oncotic pressure (e.g., hypoalbuminemia)
3. Exudative effusions
   a. Pathophysiology: caused by increased permeability of pleural surfaces or decreased lymphatic flow from pleural surface because of damage to pleural membranes or vasculature (see Clinical Pearl 2-4)
   b. If an exudative effusion is suspected, perform the following tests on the pleural fluid: differential cell count, total protein, LDH, glucose, pH, amylase, triglycerides, microbiology, and cytology
   c. Exudative effusions meet at least one of the following of Light's criteria (transudates have none of these):
      - Protein (pleural)/protein (serum) >0.5
      - LDH (pleural)/LDH (serum) >0.6
      - LDH >two-thirds the upper limit of normal serum LDH

Quick HIT

If the patient has minimal lung compromise, pleural effusions are well tolerated, whereas pleural effusion in the presence of lung disease may lead to respiratory failure.



A B

FIGURE 2-7 **A: Upright chest radiograph showing blunting of the right costophrenic angle, typical of a small right pleural effusion (this patient had chronic liver disease). B: Chest radiograph showing left pleural effusion.**
(Reprinted with permission from Stern EJ, White CS. *Chest Radiology Companion*. Lippincott Williams & Wilkins; 1999:375, Figure 22-1A; 376, Figure 22-2A.)

Quick HIT

Pleural Fluid Pearls

- Elevated pleural fluid amylase: esophageal rupture, pancreatitis, malignancy
- Milky, opalescent fluid: **chylothorax** (lymph in the pleural space)
- Frankly purulent fluid: **empyema** (pus in the pleural space)
- Bloody effusion: malignancy
- Exudative effusions that are primarily lymphocytic: TB
- pH <7.2: **parapneumonic effusion** or empyema

B. Causes

1. CHF is the most common cause

2. Pneumonia (bacterial)
3. Malignancies: lung (36%), breast (25%), lymphoma (10%)
4. Pulmonary embolism (PE)
5. Viral diseases
6. Cirrhosis with ascites (also known as hepatic hydrothorax)

CLINICAL PEARL 2-4

Causes of Transudative and Exudative Pleural Effusions

Transudative

- CHF
- Cirrhosis
- PE
- Nephrotic syndrome
- Peritoneal dialysis
- Hypoalbuminemia
- Atelectasis

Exudative

- Bacterial pneumonia, TB
- Malignancy, metastatic disease
- Viral infection
- PE
- Collagen vascular diseases

C. Clinical Features

1. Symptoms
   a. Often asymptomatic
   b. Dyspnea on exertion
   c. Peripheral edema
   d. Orthopnea, paroxysmal nocturnal dyspnea
2. Signs
   a. Dullness to percussion
   b. Decreased breath sounds over the effusion
   c. Decreased tactile fremitus

Quick HIT

If pleural fluid glucose level is <60, consider rheumatoid arthritis. However, glucose in pleural fluid can be low with other causes of pleural effusion: empyema, TB, esophageal rupture, malignancy, lupus.

D. Diagnosis

Can confirm presence/evaluate size of effusion by the following:

1. CXR (PA and lateral)—look for the following:
   a. Blunting of costophrenic angle
   b. About 250 mL of pleural fluid must accumulate before an effusion can be detected.
   c. Lateral decubitus films: more reliable than PA and lateral CXRs for detecting small pleural effusions; can also determine whether fluid is free flowing or loculated
2. Point-of-care ultrasound—more reliable than CXR for detecting small effusions and can be used for image-guided thoracentesis. Fluid will appear hypoechoic or black (see Figure 2-8)
3. CT chest—more reliable than CXR for detecting effusions
4. Thoracentesis
   a. Thoracentesis is indicated for evaluation of all new pleural effusions. It provides a diagnosis in 75% of patients, and even when it is not diagnostic, it provides important clinical information
   b. Therapeutic—drainage provides relief for large effusions
   c. Pneumothorax is a complication seen in 10% to 15% of thoracenteses (reduced to <3% if ultrasound guidance is used), but it requires treatment with a chest tube in <5% of cases

E. Treatment

1. Transudative effusions
   a. Diuretics and sodium restriction
   b. Therapeutic thoracentesis—only if massive effusion is causing dyspnea
2. Exudative effusions: treat underlying disease
3. Parapneumonic effusions (pleural effusion in presence of pneumonia)
   a. Uncomplicated effusions: antibiotics alone (in most cases)

b. Complicated effusions or empyema

- Chest tube drainage
- Intrapleural injection of fibrinolytic agents (streptokinase, urokinase, or tissue plasminogen activator [tPA]); may accelerate the drainage
- Surgical lysis of adhesions may be required

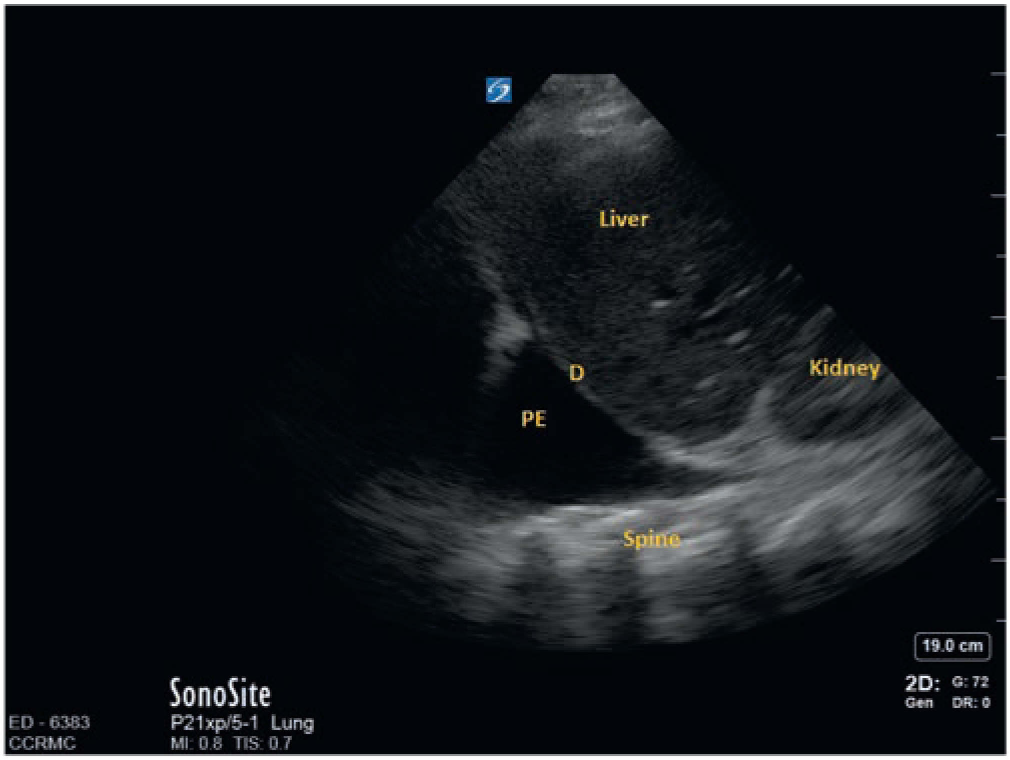


FIGURE 2-8 **Ultrasound demonstrating pleural effusion. D, diaphragm; PE, pleural effusion. Pleural fluid appears anechoic (*black*). The "spine sign" is present, as the spine is visible extending behind the effusion (normally, spine is not visible distal to aerated lung tissue on ultrasound due to artifact).**

(Reprinted with permission from Bornemann P. *Ultrasound for Primary Care*. Wolters Kluwer; 2020. Figure 13-6.)

A 49-year-old man is hospitalized with fever, shortness of breath, and a productive cough containing rust-colored sputum. On examination, he has dullness to percussion over the right lung base. Thoracentesis is performed with removal of 1.5 L of fluid. The results of laboratory tests and pleural fluid studies are shown below.

Glucose	120 mg/dL
Total protein	6.8 g/dL
LDH	75 U/L
Pleural fluid studies	
pH	6.90
Cell differential	7,300/mm^3 (89% neutrophils)
Gram stain and culture	pending
Total protein	6.0 g/dL
LDH	240 U/L
Glucose	40 mg/dL

He is started on empiric antibiotics for community-acquired pneumonia. Which of the following is the most appropriate next step in management?

A. Observation
B. Drainage with a chest tube
C. Broaden the antibiotic coverage
D. Alteplase and dornase
E. Video-assisted thoracoscopic surgery (VATS)

- **The answer is B: Drainage with a chest tube.** The pleural fluid studies meet Light's criteria for an exudative process. The next step is to figure out whether the parapneumonic effusion is complicated or uncomplicated, since this will help to determine the appropriate

management. A complicated parapneumonic effusion is defined as a pH <7.2, glucose <60 mg/dL, or a positive Gram stain or culture. If gross pus is removed from the pleural space, then it is likely infected and called an empyema. Uncomplicated effusions typically resolve with antibiotics alone; however, complicated effusions require drainage. The best option for these patients is to drain the effusion with a chest tube. **(A)** Observation alone is not appropriate. **(C)** In the absence of risk factors for multidrug-resistant organisms, there is no indication to broaden the initial antibiotics. **(D)** Alteplase and dornase are used in the treatment of complicated effusions that fail to drain adequately with chest tube alone, and they are injected into the pleural space through a chest tube. **(E)** Chest tube placement is preferred to more invasive procedures such as VATS. VATS is performed by thoracic surgeons and is indicated if the effusion does not resolve with other measures (chest tubes, intrapleural lytic agents, etc.).

Empyema

A. Causes

1. Exudative pleural effusions, if left untreated, can lead to empyema (pus within the pleural space).
2. Most cases occur as a complication of bacterial pneumonia, but other foci of infection can also spread to the pleural space (e.g., mediastinitis, abscess).

B. Clinical Features

The clinical features are those of the underlying disease (pneumonia most common).

Quick HIT

- An uncomplicated parapneumonic effusion is a noninfected pleural effusion secondary to bacterial pneumonia.
- An empyema is a complicated parapneumonic effusion, which means the pleural effusion is infected.

C. Diagnosis

CXR and CT scan of the chest are the recommended tests.

D. Treatment

1. Treat empyema with aggressive drainage of the pleura (via thoracentesis) and antibiotic therapy.
2. The infection is very difficult to eradicate, and recurrence is common, requiring repeated drainage.
3. If empyema is severe and persistent, rib resection and open drainage may be necessary.

Pneumothorax

A. General Characteristics

1. Defined as air in the normally airless pleural space
2. There are two major categories: spontaneous and traumatic pneumothoraces
3. Traumatic pneumothoraces are often iatrogenic
4. Spontaneous pneumothorax occurs without any trauma
   a. Primary spontaneous pneumothorax
      - Occurs without any underlying lung disease—that is, in "healthy" individuals
      - Caused by spontaneous rupture of subpleural blebs (air-filled sacs on the lung) at the apex of lungs—escape of air from the lung into pleural space causes lung to collapse
      - More common in tall, lean young men
      - These patients have sufficient pulmonary reserve, so severe respiratory distress does not occur in most cases

- Recurrence rate is lower, around 30% at 5 years

b. Secondary spontaneous pneumothorax
- Occurs as a complication of underlying lung disease, most commonly COPD; other underlying conditions include asthma, interstitial lung disease (ILD), neoplasms, CF, and tuberculosis (TB)
- Is more life threatening because of lack of pulmonary reserve in these patients
- Often requires definitive intervention such as pleurodesis to prevent recurrence

Quick HIT

Secondary spontaneous pneumothorax has a high recurrence rate, so definitive intervention is often needed.

B. Clinical Features

1. Symptoms
   a. Ipsilateral chest pain, usually sudden in onset
   b. Dyspnea
   c. Cough
2. Physical signs
   a. Decreased breath sounds over the affected side
   b. Hyperresonance over the chest
   c. Decreased or absent tactile fremitus on the affected side
   d. Mediastinal shift toward the side of the pneumothorax

C. Diagnosis

CXR confirms the diagnosis in stable patients—shows the visceral pleural line (see Figure 2-9).
Pleural ultrasound can be used for rapid bedside evaluation (e.g., unstable patients)—shows lack of lung sliding, presence of lung point.

D. Treatment

1. Primary spontaneous pneumothorax

a. If small and patient is asymptomatic:
  - Observation—should resolve spontaneously in approximately 10 days
  - Small chest tube (with one-way valve) may benefit some patients

b. If pneumothorax is larger and/or patient is symptomatic:
  - Administration of supplemental oxygen, which helps with resorption of pleural air
  - Needle aspiration or chest tube insertion to allow air to be released and lung to reexpand

2. Secondary spontaneous pneumothorax—chest tube drainage

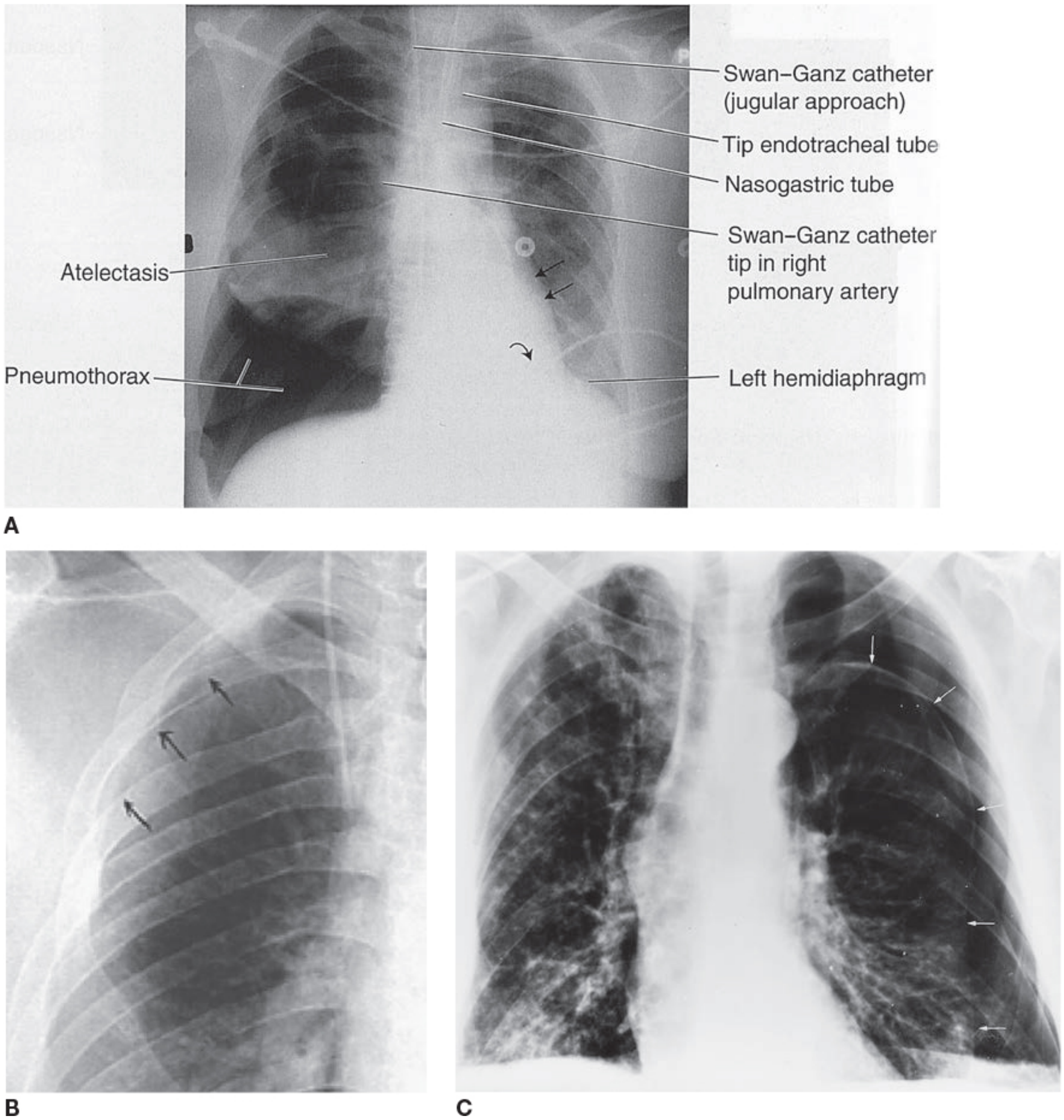


FIGURE 2-9 **A: Right pneumothorax seen in a patient on a ventilator, with *black arrows* indicating mediastinal shift. B: Chest radiograph showing a right pneumothorax (*black arrows*) that occurred as a complication of placement of a central line. These small pneumothoraces are often difficult to detect. C: Large left pneumothorax (*white arrows*).**
(**A** reprinted with permission from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Lippincott-Raven; 1998:100. Figure 6-41B. **B** reprinted with permission from Stern EJ, White CS. *Chest Radiology Companion*. Lippincott Williams & Wilkins; 1999:381. Figure 22-9. **C** reprinted with permission from Stern EJ, White CS. *Chest Radiology Companion*. Lippincott Williams & Wilkins; 1999:381. Figure 22-9.)

Tension Pneumothorax

A. General Characteristics

1. Accumulation of air within the pleural space such that tissues surrounding the opening into the pleural cavity act as valves, allowing air to enter but not to escape.
2. The accumulation of air under (positive) pressure in the pleural space **collapses the ipsilateral lung** and **shifts the mediastinum away** from the side of the pneumothorax.

B. Causes

1. Mechanical ventilation with associated barotrauma
2. Cardiopulmonary resuscitation
3. Trauma

C. Clinical Features

1. Hypotension—cardiac filling is impaired due to compression of the great veins
2. Distended neck veins
3. Shift of trachea **away** from the side of the pneumothorax on CXR (see Figure 2-10)
4. Decreased breath sounds on the affected side
5. Hyperresonance to percussion on the side of the pneumothorax

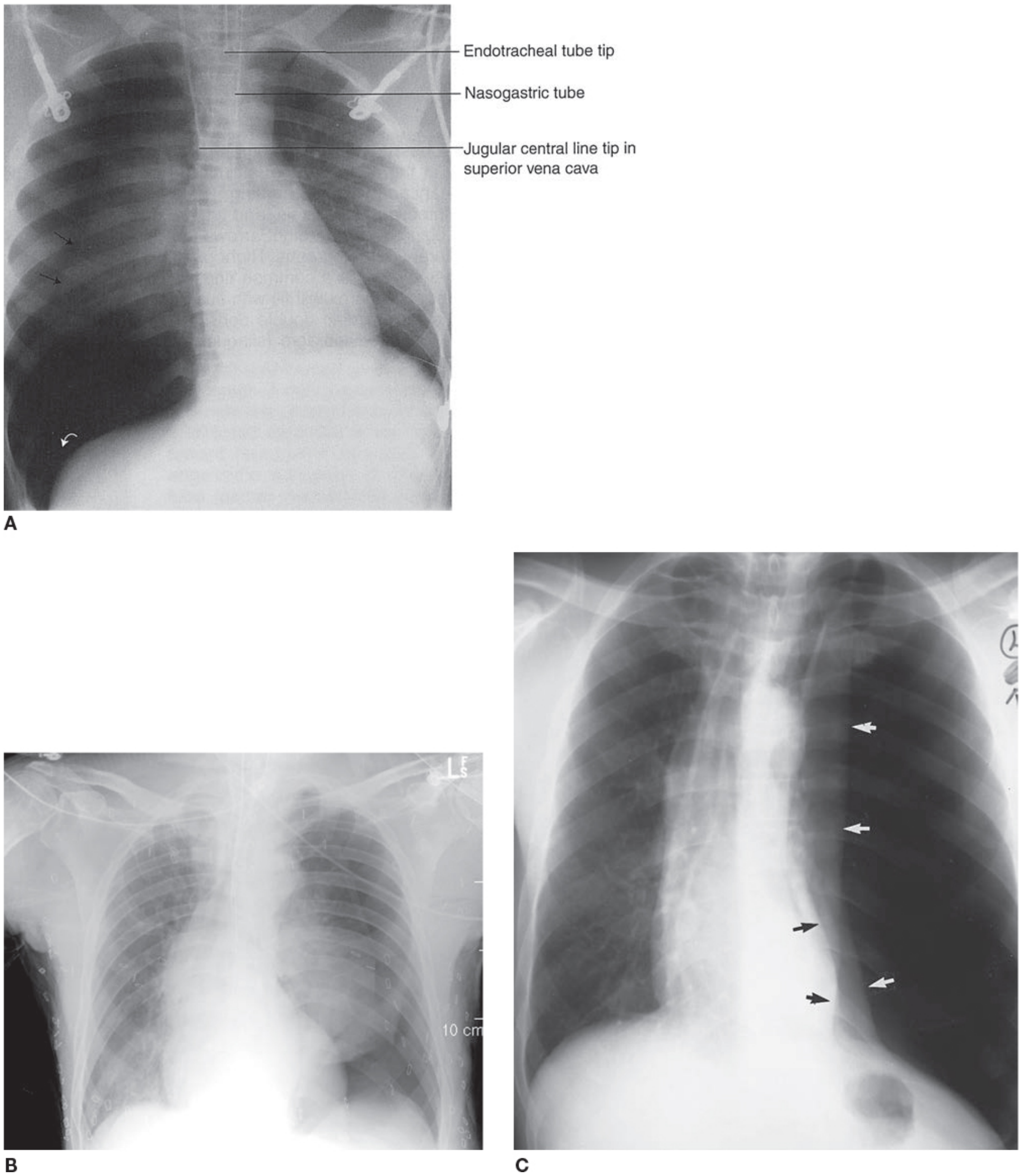


FIGURE 2-10 **A: Example of a right tension pneumothorax. Note that the mediastinum is displaced to the left. B: Left tension pneumothorax. C: Left tension pneumothorax (*white arrows*) with mediastinal shift (*black arrows*).**
(**A** reprinted with permission from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Lippincott-Raven; 1998:100. Figure 6-41C. **B** reprinted with permission from Mergo PJ. *Imaging of the Chest—A Teaching File*. Lippincott Williams & Wilkins; 2002:258. Figure 145. **C** reprinted with permission from Topol EJ. *Textbook of Cardiovascular Medicine*. 2nd ed. Lippincott Williams & Wilkins; 2002:1050. Figure 47.2.)

D. Treatment

1. Must be treated as a **medical emergency**—if the tension in the pleural space is not relieved, the patient is likely to die of hemodynamic compromise (inadequate cardiac output or hypoxemia).
2. Immediately perform chest decompression with a large-bore needle followed **immediately** by chest tube placement. There are multiple approaches. Anterior: in the second or third intercostal space in the midclavicular line. Lateral approach: fifth intercostal space along midaxillary line of affected side.

Quick HIT

Do not obtain CXR if a tension pneumothorax is suspected. Immediately decompress the pleural space via large-bore needle or chest tube!

Quick HIT

Not all mesotheliomas are malignant. Benign mesotheliomas have an excellent prognosis (and are unrelated to asbestos exposure).

Malignant Mesothelioma

- Most cases are secondary to asbestos exposure.
- Dyspnea, weight loss, and cough are common findings.
- Bloody effusion is common.
- Prognosis is dismal (few months’ survival).

Interstitial Lung Disease

Overview

A. General Characteristics

1. ILD is defined as an inflammatory process involving the alveolar wall (resulting in widespread fibroelastic proliferation and collagen deposition) that can lead to irreversible fibrosis, distortion of lung architecture, and impaired gas exchange.
2. The prognosis is highly variable and depends on the diagnosis.
3. Patients with environmental or occupational lung disease, especially those with asbestosis, are frequently involved in lawsuits against their employers.

Quick HIT

If ILD is suspected, ask about the following:

- Medication and radiation history, as some drugs are known to be toxic to lungs (chemotherapeutic agents, illicit drugs, amiodarone, certain antibiotics, many others)
- Previous jobs, because occupational exposure is a cause of ILD (asbestos, silicone, beryllium, coal)
- Past medical history, as many conditions are associated with ILD (connective tissue disease, inflammatory bowel disease, allergic rhinitis/asthma, or malignancy)
- Smoking history, as some types of ILD only occur among current or former smokers

B. Classification

1. Classified based on pathologic and clinical characteristics
2. Environmental lung disease
   a. Coal worker's pneumoconiosis
   b. Silicosis
   c. Asbestosis
   d. Berylliosis
3. ILD associated with granulomas

a. Sarcoidosis—other organs in addition to the lungs are involved
b. Langerhans cell histiocytosis (PLCH; eosinophilic granulomatosis)
c. Granulomatosis with polyangiitis (GPA)
d. Eosinophilic granulomatosis with polyangiitis (EGPA)

4. Alveolar filling disease
   a. Anti-glomerular basement membrane (GBM, Goodpasture) disease
   b. Idiopathic pulmonary hemosiderosis
   c. Pulmonary alveolar proteinosis
5. Hypersensitivity lung disease
   a. Hypersensitivity pneumonitis
   b. Eosinophilic pneumonia
6. Drug-induced—amiodarone, nitrofurantoin, bleomycin, phenytoin, illicit drugs
7. Miscellaneous
   a. Idiopathic pulmonary fibrosis
   b. Cryptogenic organizing pneumonia (COP)
   c. ILD associated with connective tissue disorders: rheumatoid arthritis, scleroderma, systemic lupus erythematosus, mixed connective tissue disease
   d. Radiation pneumonitis

***Quick* HIT**

Over 100 causes of ILD have been identified.

- In general, the clinical findings and imaging study results are nonspecific and do not point to a definitive diagnosis. Often one is confronted with the question of whether to obtain a tissue biopsy.

FIGURE **2-11** **Clubbing of the finger.**
(Reprinted with permission from *Stedman's Medical Dictionary*. 28th ed. Lippincott Williams & Wilkins; 2005.)

C. Clinical Features

1. Symptoms
   a. Dyspnea (at first with exertion; later at rest)
   b. Cough (nonproductive)
   c. Fatigue
   d. Other symptoms may be present secondary to another condition (such as a connective tissue disorder)
2. Signs
   a. Dry "velcro-like" crackles at the bases are common
   b. Digital clubbing is common in some types, often late manifestation (especially with idiopathic pulmonary fibrosis) (see Figure 2-11 and Clinical Pearl 2-5)
   c. Signs of pulmonary HTN and cor pulmonale (augmented P2 on cardiac auscultation, peripheral edema) in advanced disease
   d. Cyanosis in advanced disease

D. Diagnosis

1. CXR
   a. Findings are usually nonspecific
   b. Typical diffuse changes are noted (reticular, reticulonodular, ground glass, honeycombing)
2. HRCT scan shows the extent of fibrosis better than other imaging modalities (see Figure 2-12)
3. PFTs
   a. A restrictive pattern is noted: All lung volumes are low. Both FEV_1 and FVC are reduced, but the ratio is often preserved so FEV_1/FVC ratio is normal or increased
   b. Low diffusing capacity (DL_{CO})
4. Oxygen desaturation during exercise
5. Bronchoalveolar lavage (fluid for culture and cytology)—use is controversial because results are quite variable
6. Tissue biopsy
   a. This may be required in patients with ILD when diagnosis cannot be made by appearance on HRCT and PFTs.
   b. This can be done via flexible bronchoscopy with transbronchial biopsy (a limited amount of tissue can be obtained, which limits its utility), open lung biopsy, or video-assisted thoracoscopic lung biopsy.
7. Urinalysis, if there are signs of glomerular injury (for Goodpasture syndrome and GPA)

CLINICAL PEARL 2-5

Clubbing of the Fingers

- Increased convexity of the nail—the distal phalanx is enlarged due to an increase in soft tissue.
- If a patient has clubbing, get a CXR because lung disease may be present.
- Chronic hypoxia is the underlying cause in most cases.
- Differential diagnoses vary and include pulmonary diseases (lung cancer, CF, ILD, empyema, sarcoidosis, and mesothelioma), congenital heart disease, bacterial endocarditis, biliary cirrhosis, inflammatory bowel disease, and primary biliary cirrhosis.
- Digital clubbing may be an idiopathic or primary finding, such as in familial clubbing or hypertrophic osteoarthropathy.

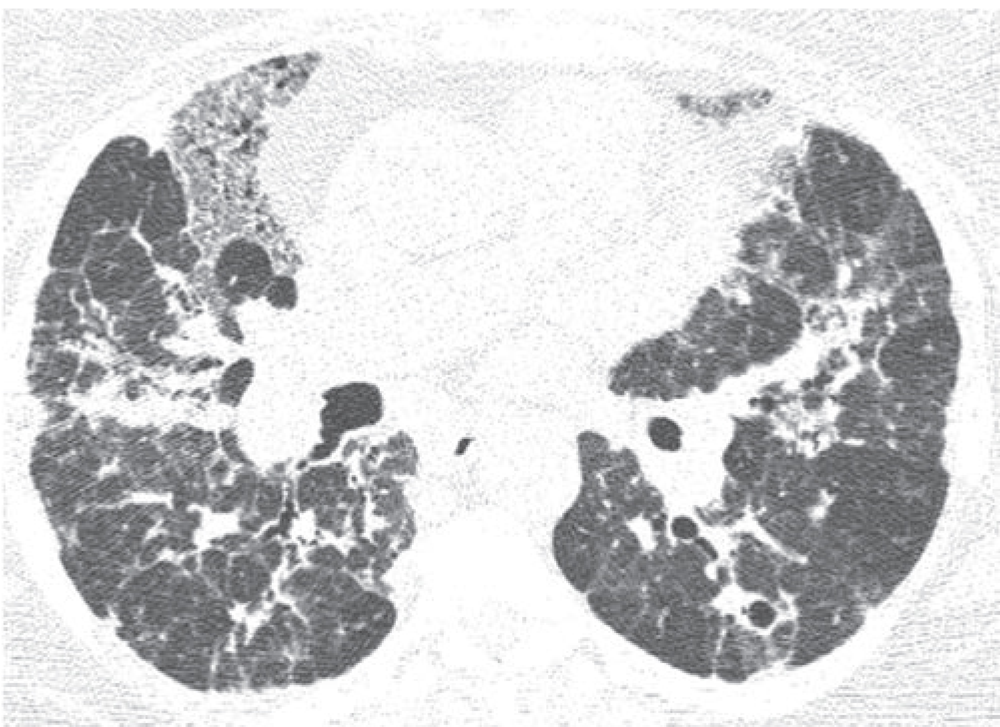


FIGURE 2-12 **Example of interstitial lung disease: Chest CT shows extensive pulmonary fibrosis.**
(Reprinted with permission from Elicker BM, Webb WR. *Fundamentals of High-Resolution Lung CT: Common Findings, Common Patterns, Common Diseases, and Differential Diagnosis*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013. Figure 2-26B.)

Quick HIT

"Honeycomb lung" refers to a scarred shrunken lung and is an end-stage finding with poor prognosis. Air spaces are dilated, and there are fibrous scars in the interstitium. It can arise from many different types of ILD.

A 52-year-old woman presents with progressive shortness of breath and a chronic dry cough. Initially, she presented to her primary care provider and had a CXR performed which showed prominent reticular markings in the lung fields. She has no relevant medical history and does not take any medications. She denies any fevers, weight loss, or chest pain. There is a family history of hypertension and dyslipidemia, but no lung or heart disease. She works as a receptionist and has never smoked. On physical examination, there are dry rales throughout both lung fields with scattered wheezes. There is no focal dullness to percussion. Initial laboratory tests are ordered and show a normal hemoglobin and leukocyte count, as well as normal electrolytes and liver enzymes. HIV testing is performed and is negative.

Which of the following should be done next in the workup of this patient?

A. High-resolution computed tomography
B. CXR
C. Lung tissue biopsy
D. Bronchoscopy

- **The answer is A: High-resolution computed tomography.** Diffuse dry rales (crackles) indicate an interstitial lung process such as pulmonary fibrosis. High-resolution CT scans help to make the diagnosis of interstitial lung disease and to differentiate among the various subtypes. **(B)** A CXR was recently performed on this patient, and repeating this study is unlikely to yield any new information. **(C)** Biopsy of the lung is a very invasive procedure. It may be performed eventually on this patient, but the next step is further imaging to characterize the lung pathology. **(D)** Bronchoscopy is also an invasive test and would not be indicated as an initial workup.

Quick HIT

- Up to two-thirds of patients with sarcoidosis experience resolution/improvement of symptoms over several years.
- Approximately 20% of patients develop chronic disease.
- From 10% to 20% of patients are asymptomatic but have CXR findings.

Interstitial Lung Diseases Associated With Granulomas

A. Sarcoidosis

1. **General characteristics**
   a. A chronic systemic granulomatous disease characterized by **noncaseating granulomas**, often involving multiple organ systems. Lungs are almost always involved. Etiology unknown.
   b. Highest prevalence is in Black Americans, especially women.
   c. Seventy-five percentage of cases occur when the individual is <40 years of age.
   d. Sarcoidosis carries a good prognosis in majority of patients.
2. **Clinical features**
   a. Constitutional symptoms
      - Malaise, fever, anorexia, weight loss
      - Symptoms vary in severity and may be absent in many patients.
   b. Lungs: dry cough, dyspnea (especially with exercise), chest pain
   c. Skin (25% of cases)
      - **Erythema nodosum**
      - Plaques, subcutaneous nodules, maculopapular eruptions
   d. Eyes (25% of cases)—may result in significant visual impairment
      - **Anterior uveitis** (75%)
      - Posterior uveitis (25%)
      - Conjunctivitis
   e. Musculoskeletal system (25% to 50%)
      - Arthralgias and arthritis
      - Bone lesions

f. Heart (5% of cases)
- Arrhythmias
- Conduction disturbances, such as heart block
- Heart failure
- Sudden death

g. Nervous system (5%)
- Cranial mononeuropathy (Bell palsy is common)
- Optic neuropathy
- Hypothalamic or pituitary abnormalities
- Peripheral neuropathy

Quick HIT

Cardiac disease is the most common cause of death, although it is not a common finding.

3. **Diagnosis**

a. Diagnosis is based on clinical, radiographic, and histologic findings.

b. CXR—**Bilateral hilar adenopathy** is the hallmark of this disease but is not specific; it is seen in 50% of cases (see Figure 2-13). Four stages have been described based on CXR findings (see below).

c. Skin anergy with tuberculin skin test—typical finding but not diagnostic.

d. **Angiotensin-converting enzyme (ACE)** is elevated in serum in about 75% of patients. This test helps support the diagnosis. However, other pulmonary diseases may cause an elevation in this enzyme (lacks sensitivity and specificity).

e. Hypercalciuria and hypercalcemia are common.

f. Definitive diagnosis requires transbronchial biopsy:
- Must see **noncaseating granulomas**
- By itself is not diagnostic because noncaseating granulomas are found in other diseases
- Must be used in the context of clinical presentation

g. PFTs: decreased lung volumes (VC and TLC), decreased DL_{CO} (diffusing capacity for carbon monoxide), decreased or normal FEV_1/FVC ratio

Quick HIT

Typical presentation of sarcoidosis: young patient with constitutional symptoms, respiratory complaints, erythema nodosum, blurred vision, and bilateral hilar adenopathy.

4. **Staging of sarcoidosis (on CXR)**
   a. Stage I: bilateral hilar adenopathy without parenchymal infiltrates (highest rate of remission)
   b. Stage II: hilar adenopathy with parenchymal infiltrates
   c. Stage III: diffuse parenchymal infiltrates without hilar adenopathy (least favorable prognosis)
   d. Stage IV: pulmonary fibrosis with honeycombing and fibrocystic parenchymal changes
5. **Treatment**
   a. Most cases resolve or significantly improve spontaneously in 2 years and do not require treatment.
   b. **Systemic corticosteroids are the treatment of choice**. The indications for treatment are unclear. However, patients who are symptomatic or have active lung disease, pulmonary function deterioration, conduction disturbances, or severe skin or eye involvement should be treated.
   c. Methotrexate or other immunosuppressive agents can be used in patients with progressive disease refractory to corticosteroids.

FIGURE 2-13 **Chest radiograph in a patient with sarcoidosis. Note enlargement of mediastinal and hilar lymph nodes, as well as diffuse interstitial disease, especially on the left.**
(Reprinted with permission from Daffner RH. *Clinical Radiology: The Essentials*. 2nd ed. Lippincott Williams & Wilkins; 1999:140. Figure 4.75B.)

B. Pulmonary Langerhans Cell Histiocytosis

1. Rare chronic interstitial pneumonia caused by abnormal proliferation of histiocytes (related to Langerhans cells of the skin).
2. Most patients (90%) are cigarette smokers.
3. Variants of disease include eosinophilic granuloma (localized to bone or lung), and two systemic forms—Letterer–Siwe disease and Hand–Schüller–Christian syndrome.
4. Common findings include dyspnea and nonproductive cough.
5. Other possible manifestations are spontaneous pneumothorax, lytic bone lesions, and diabetes insipidus.
6. CXR has a honeycomb appearance, and CT scan shows cystic lesions.

7. The prognosis and course are highly variable. Smoking cessation is important. Corticosteroids are sometimes effective. Lung transplantation may be necessary.

C. Granulomatosis With Polyangiitis

1. Rare disease with unknown etiology.
2. Characterized by necrotizing granulomatous vasculitis.
3. Affects vessels of lungs, kidneys, upper airway, skin, and sometimes other organs.
4. Manifestations of the disease include upper and lower respiratory infections, glomerulonephritis, and pulmonary nodules.
5. The gold standard for diagnosis is tissue biopsy, but if the patient tests positive for c-antineutrophil cytoplasmic antibodies, the likelihood of having this condition is high.
6. Treatment usually includes glucocorticoids and immunosuppressants.

***Quick* HIT**

Antineutrophil cytoplasmic antibodies (ANCA) and associated ILD: c-ANCA is associated with GPA; **p-ANCA** is associated with EGPA; may also be positive in anti-GBM antibody or Goodpasture disease.

D. Eosinophilic Granulomatosis With Polyangiitis

1. Granulomatous vasculitis is **seen in patients with asthma**.
2. Typically presents with pulmonary infiltrates, rash, and eosinophilia.
3. Systemic vasculitis may result in skin, muscle, and nerve lesions.
4. Diagnosis: Based on clinical findings in association with significant eosinophilia.
5. Associated with perinuclear antineutrophil cytoplasmic antibody.
6. Treat with systemic glucocorticoids and other immunosuppressants (cyclophosphamide).

Environmental Lung Disease/Pneumoconiosis

A. Coal Worker's Pneumoconiosis

1. Most have simple coal worker's pneumoconiosis, which usually causes no significant respiratory disability.
2. Some patients may develop complicated pneumoconiosis, which is characterized by fibrosis (restrictive lung disease).
3. Causes: inhalation of coal dust, which contains carbon and silica.

Quick HIT

- Pneumoconiosis is defined as the accumulation of dust in the lungs, and the tissue reaction to its presence.
- Dusts that have been implicated: silica, beryllium, asbestos, coal dust, graphite, carbon black, aluminum, talc.

B. Asbestosis

1. Characterized by diffuse interstitial fibrosis of the lung caused by inhalation of asbestos fibers; predilection for lower lobes.
2. Develops insidiously many years (>15 to 20 years) after exposure.
3. **Increased risk of bronchogenic carcinoma (smoking is synergistic) and malignant mesothelioma.**
4. Symptoms and physical findings are nonspecific (see above under ILD).
5. Diagnosis made based on imaging findings and history of exposure to asbestos.
6. CXR shows hazy infiltrates with bilateral linear opacities and may show pleural plaques (especially in lower lung regions). HRCT is more sensitive to detect abnormalities (usually pleural plaques, honeycombing in advanced disease).
7. No specific treatment is available. Focus on preventing complications (smoking cessation, immunizations).

Quick HIT

Classic CXR findings in environmental lung disease:

- Asbestosis: pleural plaques
- Silicosis: “eggshell” calcifications

C. Silicosis

1. **Localized** and **nodular** peribronchial fibrosis (upper lobes more common).
2. Can be acute (massive exposure leading to rapid onset and death), or chronic (symptoms years after exposure—up to 15 years or longer).
3. Associated with an increased risk of TB.
4. **Sources include mining, sandblasting, stone cutting, and glass manufacturing.**
5. Exertional dyspnea is the main symptom; cough with sputum is also seen.
6. PFTs will show restrictive lung disease.
7. Treatment is supportive and involves removal from exposure to silica.

D. Berylliosis

1. Like silicosis, berylliosis has acute and chronic forms.
2. Acute disease is a diffuse pneumonitis caused by massive exposure to beryllium.
3. Chronic disease is very similar to sarcoidosis: granulomas, skin lesions, and hypercalcemia may be present.
4. The beryllium lymphocyte proliferation test is a useful diagnostic blood test.
5. Give glucocorticoid therapy for both acute and chronic berylliosis.

Quick HIT

Some causes of hypersensitivity pneumonitis:

- Farmer’s lung (moldy hay)
- Bird-breeder’s lung (avian droppings)
- Air-conditioner lung
- Bagassosis (moldy sugar cane)
- Mushroom worker’s lung (compost)

Interstitial Lung Disease Associated With Hypersensitivity

A. Hypersensitivity Pneumonitis (Extrinsic Allergic Alveolitis)

1. Inhalation of an antigenic agent to the alveolar level induces an immune-mediated pneumonitis. Chronic exposure may lead to restrictive lung disease.
2. A variety of organic dusts and chemicals have been implicated.
3. The presence of serum IgG and IgA in the inhaled antigen is a hallmark finding, although many may have these antibodies without developing disease.
4. The acute form has flu-like features (e.g., fever, chills, cough, dyspnea). CXR during the acute phase shows pulmonary infiltrates.
5. The chronic form is more insidious and more difficult to diagnose.
6. Treatment involves removal of the offending agent and sometimes glucocorticoids.

B. Eosinophilic Pneumonia

1. Fever and peripheral eosinophilia are features.
2. Eosinophilic pneumonia may be acute or chronic.
3. CXR shows peripheral pulmonary infiltrates.
4. Treatment with glucocorticoids is usually very effective, but relapses may occur.

C. Note that there is significant overlap between this category and the ILD associated with granuloma (e.g., EGPA).

Alveolar Filling Disease

A. Anti-GBM Antibody or Goodpasture Disease

1. Autoimmune disease caused by IgG antibodies directed against glomerular and alveolar basement membranes (type II hypersensitivity reaction).
2. Results in hemorrhagic pneumonitis and glomerulonephritis.
3. Ultimately, renal failure is a complication of proliferative glomerulonephritis.
4. Usually presents with hemoptysis and dyspnea.
5. Diagnosis made by tissue biopsy, serologic evidence of anti-GBM antibodies.
6. Prognosis is poor; treat with plasmapheresis, cyclophosphamide, and corticosteroids.

B. Pulmonary Alveolar Proteinosis

1. Rare condition caused by accumulation of surfactant-like protein and phospholipids in the alveoli.
2. Usually presents with dry cough, dyspnea, hypoxia, and rales.
3. **CXR typically has a ground-glass appearance with bilateral alveolar infiltrates that resemble a bat wing shape.** CT will show ground-glass opacifications with thickened interlobular septa in polygonal shapes, as known as "crazy-paving."
4. Lung biopsy or bronchoalveolar lavage fluid is required for definitive diagnosis.
5. Treatment is with lung lavage and granulocyte colony–stimulating factor.
6. Patients are at increased risk of infection, and corticosteroids should not be given (may increase mortality).

Miscellaneous Interstitial Lung Diseases

A. Idiopathic Pulmonary Fibrosis

1. **General characteristics**
   a. Etiology unknown; more common in men, smokers, age >60.
   b. Presents with gradual onset of progressive dyspnea, nonproductive cough.
   c. This is a devastating and unrelenting disease. Although the prognosis is variable, the mean survival is only 3 to 7 years after first diagnosis.
2. **Diagnosis**
   a. CXR: ground-glass or a honeycombed appearance; may be normal.
   b. HRCT of chest: bibasilar reticular opacities, honeycombing, and traction bronchiectasis.
   c. Diagnosis can be made by clinical features in combination with typical radiologic appearance on HRCT. If diagnosis is unclear, lung biopsy may be done to confirm histopathologic diagnosis of usual interstitial pneumonia (UIP).
   d. Other causes of ILD must be excluded.
3. **Treatment**. Options are limited. The majority of patients (>70%) do not improve with therapy and experience progressive and gradual respiratory failure. The following can benefit some patients:
   a. Supplemental oxygen.
   b. New antifibrotic agents such as nintedanib or pirfenidone have been shown in trials to slow progression of mild and moderate disease.
   c. Corticosteroids have been used historically but with little or no benefit and have significant side effects.
   d. Lung transplantation.

B. Cryptogenic Organizing Pneumonitis

1. An inflammatory lung disease with similar clinical and radiographic features to infectious pneumonia.
2. Associated with many entities (viral infections, medications, connective tissue disease). Most cases are idiopathic.
3. Features: cough, dyspnea, and flu-like symptoms; bilateral patchy infiltrates on CXR or patchy ground-glass opacities on HRCT.

4. Antibiotics have not been found to be effective.
5. Spontaneous recovery may occur, but corticosteroids are used most commonly (>60% of patients recover).
6. Relapse may occur after cessation of corticosteroids (requiring resumption).

CLINICAL PEARL 2-6

Hypoxemia Pearls

1. To determine the underlying mechanism of hypoxemia, three pieces of information are needed:
   - $PaCO_2$ level
   - A–a gradient
   - Response to supplemental oxygen
2. A–a gradient is normal, if hypoventilation or low inspired PO_2 is the only mechanism.
3. If V/Q mismatch or shunting is present, then both $PaCO_2$ and A–a gradient are elevated; response to supplemental O_2 differentiates between the two mechanisms.

C. Radiation Pneumonitis

1. Interstitial pulmonary inflammation—occurs in 5% to 15% of patients who undergo thoracic irradiation for lung cancer, breast cancer, lymphoma, or thymoma. Mortality and morbidity are related to the irradiated lung volume, dose, patient status, and concurrent chemotherapy.
2. Acute form occurs 4 to 12 weeks after irradiation; chronic form develops after 6 to 12 months—characterized by alveolar thickening and pulmonary fibrosis.
3. Features: low-grade fever, cough, chest fullness, dyspnea, pleuritic chest pain, hemoptysis, acute respiratory distress.
4. CXR is usually normal.
5. CT scan is the best study: diffuse infiltrates (hallmark) with straight-line effect conforming to area of radiation, ground-glass density, patchy/homogeneous consolidation, pleural/pericardial pleural

effusions. It is excellent for detecting recurrent cancer in irradiated area.

6. The treatment of choice is corticosteroids for symptomatic patients.

Quick HIT

- Severe hypoxemia can result in irreversible damage to organs (CNS and cardiovascular systems most affected) and must be corrected rapidly.
- Severe hypercapnia (and respiratory acidosis) can lead to dyspnea and vasodilation of cerebral vessels (with increased intracranial pressure and subsequent papilledema, headache, impaired consciousness, and finally coma).

Respiratory Failure

Acute Respiratory Failure

A. General Characteristics

1. Acute respiratory failure results when there is inadequate oxygenation of blood or inadequate ventilation (elimination of CO_2) or both (see Clinical Pearls 2-6 and 2-7). The following are general criteria used to define acute respiratory failure:
   a. Hypoxia (PaO_2 <60 mm Hg)
   b. Hypercapnia (partial pressure of CO_2 [PCO_2] >50 mm Hg)

CLINICAL PEARL 2-7

Ventilation Versus Oxygenation

- Ventilation is monitored by $PaCO_2$: To ↓ $PaCO_2$, one must either ↑ respiratory rate (RR) or ↑ tidal volume (V_T). Note that minute ventilation = RR × V_T.
- Oxygenation is monitored by O_2 saturation and PaO_2: To ↓ PaO_2 in the ventilated patient, one must either ↓ FiO_2 or ↓ PEEP.

Note that ventilation and oxygenation are unrelated. O_2 saturation may be 100% with a very high $PaCO_2$, and the patient can be in ventilatory failure!

2. The following structures or systems are essential components for maintaining normal respiration. Dysfunction or interruption of any component (causes are listed) can potentially lead to respiratory failure.
   a. CNS (brain and spinal cord) depression or insult—drug overdose, stroke, trauma
   b. Neuromuscular disease—myasthenia gravis, polio, Guillain–Barré syndrome, amyotrophic lateral sclerosis
   c. Upper airway—obstruction due to a number of causes, including stenoses, spasms, or paralysis
   d. Thorax and pleura—mechanical restriction due to kyphoscoliosis, flail chest, hemothorax, tension pneumothorax
   e. Cardiovascular system and blood—CHF, valvular diseases, PE, anemia
   f. Lower airways and alveoli—asthma, COPD, pneumonia, **acute respiratory distress syndrome** (ARDS), pulmonary edema
3. Classification—acute respiratory failure can be divided into two major types (overlap often exists)
   a. Hypoxemic respiratory failure.
      - Low PaO_2 with a $PaCO_2$ that is either low or normal—present when O_2 saturation is <90% or PaO_2 <60 mm Hg.
      - Causes include disease processes that involve the lung itself (e.g., ARDS, pneumonia, pulmonary edema).

- V/Q mismatch and intrapulmonary shunting are the major pathophysiologic mechanisms.

b. Hypercapnic (hypercarbic) respiratory failure—a failure of alveolar ventilation.
- Either a decrease in minute ventilation or an increase in physiologic dead space leads to CO_2 retention and eventually results in hypoxemia.
- May be caused by an underlying lung disease (COPD, asthma, CF, severe bronchitis).
- May also occur in patients with no underlying lung disease who have impaired ventilation due to neuromuscular diseases, CNS depression, mechanical restriction of lung inflation, or any cause of respiratory fatigue (e.g., prolonged hyperventilation in diabetic ketoacidosis).

4. Pathophysiology

a. V/Q mismatch
- Caused by a defect in either alveolar ventilation (e.g., pulmonary edema) or perfusion (e.g., PE)
- Typically leads to hypoxia **without hypercapnia** (in fact, $PaCO_2$ levels are often low or normal)
- Most common mechanism of hypoxemia (especially in chronic lung disorders)
- Responsive to supplemental oxygen

b. Shunting
- Little or no ventilation in perfused areas (due to collapsed or fluid-filled alveoli); venous blood is shunted into the arterial circulation without being oxygenated; represents one end of the spectrum in V/Q mismatch.
- Causes of shunts: atelectasis or fluid buildup in alveoli (pneumonia or pulmonary edema), direct right-to-left intracardiac blood flow in congenital heart diseases.
- **Hypoxia due to a shunt is not responsive to supplemental oxygen.**

c. Hypoventilation—leads to hypercapnia, with secondary hypoxemia

d. Increased CO_2 production (e.g., sepsis, DKA, hyperthermia) results in hypercapnic respiratory failure

e. Diffusion impairment (e.g., ILD) causes hypoxemia without hypercapnia

B. Clinical Features

1. Symptoms
   a. Dyspnea—first symptom
   b. Cough may or may not be present, depending on the underlying cause
2. Signs—the following might be present:
   a. Inability to speak in complete sentences, use of accessory muscles of respiration
   b. Tachypnea, tachycardia
   c. Cyanosis
   d. Impaired mentation (due to fatigue or hypercapnia, or if cause of respiratory failure is CNS depression)

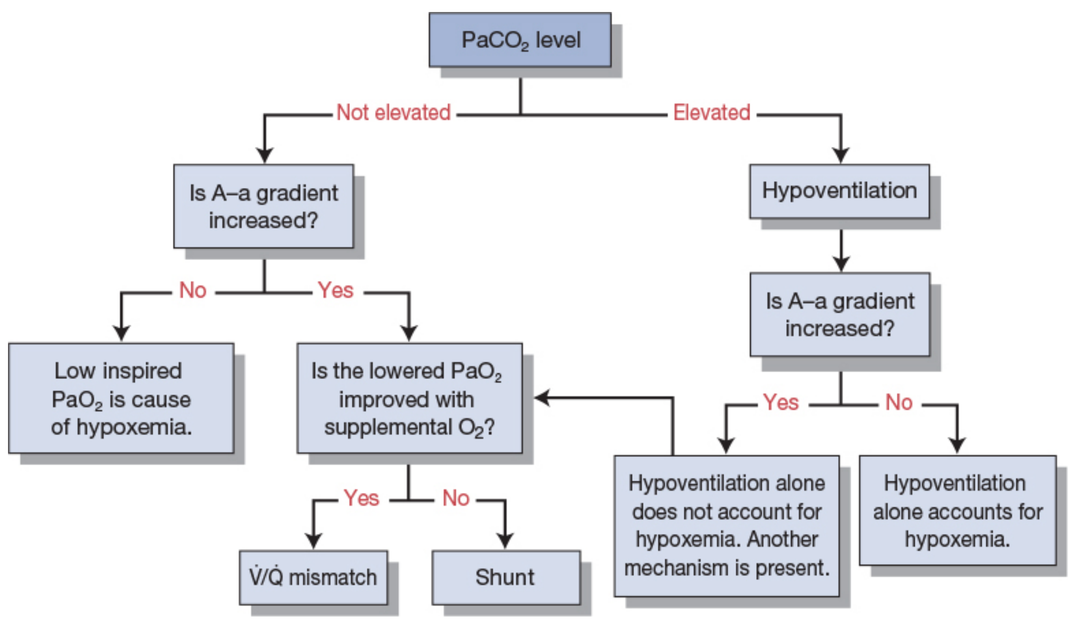


FIGURE 2-14 **Evaluation of a patient with hypoxemia.**

C. Diagnosis

1. ABG analysis—may confirm diagnosis and help severity of condition; should be obtained in most cases of respiratory failure (see Figure 2-14).

a. Hypoxemia: Mechanisms include V/Q mismatch, intrapulmonary shunting, diffusion limitation, reduced inspired FiO_2, or hypoventilation.
b. Hypercapnia: caused by hypoventilation (secondary to a variety of causes).
c. Arterial pH: Respiratory acidosis occurs when hypercapnia is present. However, if the respiratory failure is chronic, renal compensation occurs and the acidosis is less severe.

2. CXR or CT scan of the chest.
3. Complete blood count (CBC) and metabolic panel.
4. If cardiogenic pulmonary edema is suspected, check a brain natriuretic peptide (BNP) and/or cardiac enzymes.

Quick HIT

The alveolar–arterial oxygen difference (A–a gradient) is normal when hypoventilation is the cause of hypoxemia. It is increased in most other causes.

D. Treatment

1. Treat underlying disorder (e.g., with bronchodilators, corticosteroids, antibiotics, depending on the cause).
2. Provide supplemental oxygen if patient is hypoxemic (see Table 2-6 and Clinical Pearl 2-8).
   a. Hypoxemic respiratory failure: Use the **lowest concentration of oxygen** that provides sufficient oxygenation to avoid oxygen toxicity, which is due to free-radical production.
   b. Hypercapnic respiratory failure: Results from hypoventilation. In COPD patients, excessive administration of oxygen results in V/Q mismatch and the Haldane effect.
3. Apply NPPV (e.g., CPAP, BiPAP) only for **conscious** patients with possible impending respiratory failure (see Clinical Pearl 2-9). **If the patient cannot breathe on his or her own, intubate!**
4. Intubation and mechanical ventilation may be needed in both types of respiratory failure.

CLINICAL PEARL 2-8

Techniques to Improve Tissue Oxygenation

- Increase FiO_2
- Increase PEEP
- Extend inspiratory time fraction
- Decubitus, upright, or prone positioning bronchodilation
- Improve oxygen delivery: increase cardiac output or increase hemoglobin
- Decrease oxygen requirements: decrease work of breathing, fever, agitation
- Remove pulmonary vasodilators (e.g., nitroprusside)

Adapted from Baum GL, Crapo JD, Celli BR, et al., eds. *Textbook of Pulmonary Diseases*. Vol. II. 7th ed. Lippincott Williams & Wilkins; 2003. Reprinted with permission from Dr. James D. Crapo.

TABLE 2-6 Oxygen Delivery Systems

Oxygen Delivery System[a]		Flow Rate (L/min)	FiO_2 (% Oxygen)	Advantages
Low Flow	Nasal cannula	1–6	Up to 0.40	Easy to use, comfortable
	Simple face mask	5–10	0.40–0.60	Can deliver higher flow rates than nasal cannula
High Flow	Venturi mask	4–10	Up to 0.40, but can determine precise FiO_2 to deliver (24%, 28%, 31%, 35%, 40%)	Preferred in CO_2 retainers because one can more precisely control oxygenation
	Nonrebreathing mask	Up to 15	Variable, up to 0.70–0.90	Can achieve higher FiO_2 at lower flow rates
	High-flow nasal cannula	Up to 40	Up to 1.00	Higher flow rates than simple nasal cannula

[a]There are two sources of oxygen in the hospital: wall outlets and oxygen tanks (portable, large green tanks).

Quick HIT

Do not ignore hypoxia in a patient with hypercarbic respiratory failure!

Acute Respiratory Distress Syndrome

A. General Characteristics

1. ARDS is a diffuse **inflammatory process** (not necessarily infectious) involving both lungs—neutrophil activation (due to a variety of causes) in the systemic or pulmonary circulations is the primary mechanism (see Clinical Pearl 2-10).
2. ARDS is not a primary disease, but rather a disorder that arises due to other conditions that cause a widespread inflammatory process.
3. 2012 Berlin definition:
   a. Acute onset (<1 week of known clinical insult).
   b. Bilateral infiltrates on chest imaging.
   c. Pulmonary edema not explained by fluid overload or CHF (e.g., no clinical evidence of CHF or pulmonary–capillary wedge pressure [PCWP] <18 mm Hg).
   d. Abnormal PaO_2/FiO_2 ratio.
      - 200 to 300: mild ARDS
      - 100 to 200: moderate ARDS
      - <100: severe ARDS
4. Pathophysiology
   a. Massive intrapulmonary shunting of blood is a key pathophysiologic event in ARDS—severe hypoxemia with **no significant improvement on 100% oxygen (requires high PEEP to prop open airways).** Shunting is secondary to widespread atelectasis, collapse of alveoli, and surfactant dysfunction.
      - Interstitial edema and alveolar collapse are due to an increase in lung fluid, which leads to stiff lungs, an increase in alveolar–arterial oxygen difference (A–a gradient), and ineffective gas exchange.
      - Note that the **effects** of the increase in pulmonary fluid are identical to those seen in cardiogenic pulmonary edema, but the **cause** is different: An increase in alveolar–capillary permeability causes ARDS, whereas congestive hydrostatic forces cause cardiogenic pulmonary edema.
   b. Decreased pulmonary compliance—leads to increased work of breathing.

c. Increased dead space—secondary to obstruction and destruction of pulmonary–capillary bed.
d. Low vital capacity, low FRC.

CLINICAL PEARL 2-9

Noninvasive Positive Pressure Ventilation

- NPPV is delivered as either BiPAP or CPAP. BiPAP can be set at separate inspiratory and expiratory pressures (the inspiratory pressure is higher than the expiratory).
- Both can be given via nasal mask or full-face mask.
- NPPV is indicated in patients with impending respiratory failure in an attempt to avoid intubation and mechanical ventilation.
- Success rates are highest in patients with hypercapnic respiratory failure (especially COPD patients).
- Note that NPPV should not be used for life support ventilation, only to temporarily support the patient's own spontaneous breathing.
- To use NPPV, the patient must be neurologically intact, awake and cooperative, and able to protect the airway. If no improvement is seen, BiPAP should be discontinued and conventional endotracheal intubation and mechanical ventilation initiated.

CLINICAL PEARL 2-10

Remember the Following When Examining a Patient With ARDS

- Physical findings are usually nonspecific.
- Because the patient is usually intubated and on a ventilator, decreased unilateral breath sounds may be due to the ET being in the right main bronchus or possibly a pneumothorax.
- Look for potential sources of sepsis and check for any signs of infection: acute abdomen, IV lines, wounds, decubitus ulcers, etc.
- Keep in mind that cardiogenic pulmonary edema has to be distinguished from ARDS—look for signs of volume overload, CHF, JVD, edema, and hepatomegaly.

Quick HIT

Patients with sepsis or septic shock have the highest risk of developing ARDS.

Quick HIT

ARDS can progress rapidly over several hours. ARDS has a high rate of complications like barotrauma, infections, and delirium.

B. Causes

1. Sepsis is the most common risk factor—can be secondary to a variety of infections (e.g., pneumonia, urinary tract infections, wound infections)
2. Aspiration of gastric contents
3. Severe trauma, fractures (e.g., femur, pelvis), multiple or massive transfusions, near drowning
4. Acute pancreatitis
5. Drug overdose, toxic inhalations
6. Intracranial HTN
7. Cardiopulmonary bypass

C. Clinical Features

1. Dyspnea, tachypnea, and tachycardia due to increased work of breathing.
2. Progressive hypoxemia—not responsive to supplemental oxygen.
3. Patients are difficult to ventilate and at high risk for barotrauma. They often have high peak airway pressures due to stiff, noncompliant lungs.

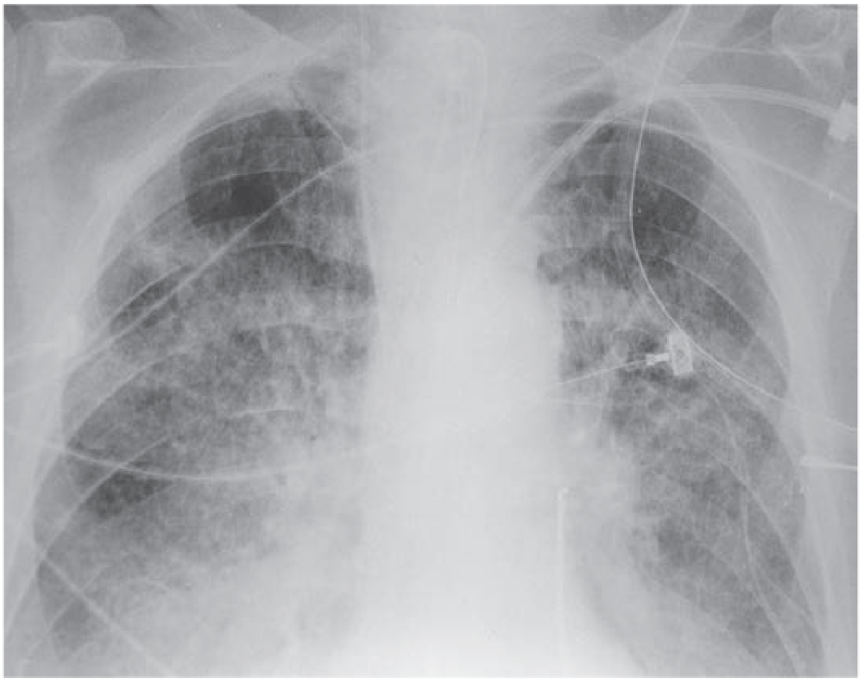
Quick HIT

2012 Berlin definition for diagnosing ARDS:

- Hypoxemia that is refractory to oxygen therapy: ratio of PaO_2/FiO_2 200 to 300 is mild, 100 to 200 is moderate, and <100 is severe
- Bilateral diffuse pulmonary infiltrates on CXR
- No evidence of CHF clinically or PCWP ≤18 mm Hg
- Respiratory symptoms that develop within 1 week of known insult

D. Diagnosis

1. CXR—**shows diffuse bilateral pulmonary infiltrates** (see Figure 2-15)
   a. There is a variable correlation between findings on CXR and severity of hypoxemia or clinical response. Diuresis improves and volume overload worsens the infiltrates—regardless of CXR findings, the underlying ARDS may or may not be improved.
   b. CXR improvement follows clinical improvement after 1 to 2 weeks or more.



A

B

FIGURE 2-15 A: Chest radiograph showing typical findings in ARDS. B: Another example of ARDS. Also note presence of an ET and Swan–Ganz central venous catheter.

(**A** reprinted with permission from Miller WT, Miller WT Jr. *Field Guide to the Chest X-Ray*. Lippincott Williams & Wilkins; 1999:4. Figure 1.2B. **B** reprinted with permission from Daffner RH. *Clinical Radiology: The Essentials*. 2nd ed. Lippincott Williams & Wilkins; 1999:175. Figure 4.117A.)

2. ABG
   a. Hypoxemia (PaO_2 <60).
   b. Initially, respiratory alkalosis ($PaCO_2$ <40) is present, which gives way to respiratory acidosis as the work of breathing increases and $PaCO_2$ increases.
   c. If the patient is septic, metabolic acidosis may be present, with or without respiratory compensation.
3. Pulmonary artery catheter—enables a determination of PCWP. PCWP reflects left heart filling pressures and is an indirect marker of intravascular volume status
   a. PCWP is the most useful parameter in differentiating ARDS from cardiogenic pulmonary edema.
   b. If PCWP is low (<18 mm Hg), ARDS is more likely, whereas if PCWP is high (>18 mm Hg), cardiogenic pulmonary edema is more likely.
   c. **However, routine placement of pulmonary artery catheters has not been shown to be beneficial in ARDS or sepsis.**
4. Bronchoscopy with bronchoalveolar lavage
   a. This may be considered if patient is acutely ill and infection is suspected.
   b. Fluid collected can be cultured and analyzed for cell differential, cytology, Gram stain, and silver stain.

E. Treatment

1. Oxygenation—try to keep O_2 saturation >90%.
2. Mechanical ventilation is based on the ARDSNet studies. The most important principles include using a high PEEP with low tidal volumes. Sedation and short-term paralysis may be needed to improve compliance with mechanical ventilation.
3. Fluid management.

a. Volume overload should be avoided. A low–normal intravascular volume is preferred; the goal should be a CVP 4 to 6 cm H_2O. Vasopressors may be needed to maintain BP.
b. On the other hand, patients with sepsis have high fluid requirements, so determining the appropriate fluid management may be difficult.

4. Treat the underlying cause, for example, infection.
5. Do not forget to address the patient's nutritional needs. Tube feedings are preferred over parenteral nutrition (see Appendix).

F. Complications

1. Permanent lung injury—resulting in lung scarring or honeycomb lung
2. Complications associated with mechanical ventilation
   a. Barotrauma secondary to high-pressure mechanical ventilation, possibly causing a pneumothorax or pneumomediastinum
   b. Nosocomial pneumonia
3. Line-associated infections: central lines and pulmonary artery catheters (line infection sepsis), urinary catheters (UTI), and nasal tubes (sinus infection)
4. Renal failure—may be due to nephrotoxic medication, sepsis with hypotension, or underlying disease
5. Ileus, stress ulcers
6. Multiorgan failure
7. Critical illness myopathy and polyneuropathy

Quick HIT

In general, err on the side of caution when deciding whether to initiate mechanical ventilation. Intubation does not mean the patient will have to remain on the ventilator indefinitely!

Mechanical Ventilation

A. General Characteristics

1. In treating respiratory failure, mechanical ventilation has two major goals: to maintain alveolar ventilation and to correct hypoxemia.

2. The decision to initiate mechanical ventilation should be a clinical one. In general, patients with the following require mechanical ventilation:
   a. Significant respiratory distress (e.g., high RR) or severe respiratory failure
   b. Impaired or reduced level of consciousness with inability to protect the airway (look for absent gag or cough reflex)
   c. Metabolic acidosis (if the patient is unable to compensate with adequate hyperventilation)
   d. Respiratory muscle fatigue
   e. Significant hypoxemia (PaO_2 <55 mm Hg despite supplemental oxygen) or hypercapnia ($PaCO_2$ >50 mm Hg); respiratory acidosis (pH <7.2) with hypercapnia
3. ABGs are used to assess response to initiation of mechanical ventilation. Acceptable ranges of gas values include a PaO_2 of 50 to 60 with $PaCO_2$ of 40 to 50, and pH between 7.35 and 7.45. In some cases (such as ARDS), permissive hypercapnia may be the goal (targeting a lower pH and higher $PaCO_2$ to avoid barotrauma).
4. General principles
   a. Initial settings should rest the respiratory muscles.
   b. The goal is to reduce the likelihood of barotrauma (high static airway pressures, overinflation) and atelectasis (low static airway pressures, underinflation).
   c. A volume-cycled ventilator is most commonly used.

B. Ventilator Settings

1. Assist control (AC) ventilation
   a. This is the initial mode used in most patients with respiratory failure.
   b. Guarantees a "backup" minute ventilation that has been preset, but the patient can still initiate breaths at a faster rate than the backup rate.
   c. AC and other ventilator modes can be volume targeted or pressure targeted. If volume targeted is selected, the ventilator will give a preset tidal volume for each breath regardless of the pressure required to give that breath (ensures ventilation but could lead to high pressures and barotrauma); if pressure targeted is selected, the ventilator will deliver a fixed inspiratory pressure regardless of the

tidal volume (avoids barotrauma but adequate ventilation may not be achieved).

d. All breaths initiated by the patient are supported by the ventilator (in contrast to intermittent mandatory ventilation).

2. Synchronous intermittent mandatory ventilation (SIMV)
   a. Patients can breathe on their own above the mandatory rate **without** help from the ventilator (i.e., the tidal volume of these extra breaths is **not** determined by the ventilator, as it is in the assist-control mode).
   b. If no spontaneous breath is initiated by the patient, the predetermined mandatory breath is delivered by the ventilator.
   c. May increase respiratory fatigue and prolonged mechanical ventilation.
3. CPAP
   a. Positive pressure (0 to 20 cm H_2O) is delivered continuously (during expiration and inspiration) by the ventilator, but no breaths are delivered (patient breathes on his or her own).
4. Pressure support ventilation (PSV)
   a. Inspiratory pressure is set to support each patient-triggered breath, with a constant PEEP. This is mostly used during weaning trials (Clinical Pearl 2-11).
5. Noninvasive mechanical ventilation
   a. CPAP: Positive pressure (0 to 20 cm H_2O) is delivered continuously (during expiration and inspiration) by the ventilator, but no breaths are delivered (patient breathes on his or her own).
   b. BiPAP: Similar to PSV but done with a face or nasal mask rather than intubation. Delivers a set inspiratory pressure with a constant PEEP.

Quick HIT

- Always confirm correct ET placement by listening for bilateral breath sounds **and** checking a postintubation CXR.
- On CXR, the tip of the ET tube should be approximately 2 to 5 cm above the carina.

C. Key Parameters

1. Settings that affect $PaCO_2$: Minute ventilation (RR × V_T)
   a. This should be adjusted to achieve the patient's baseline $PaCO_2$.
   b. An initial tidal volume (V_T) of 4 to 8 mL/kg is appropriate in most cases (lower tidal volumes are recommended in patients with ARDS and COPD).
   c. A rate of 10 to 12 breaths/min is appropriate.
2. Settings that affect PaO_2: FiO_2 and PEEP
   a. FiO_2: The initial FiO_2 should be 100%. Quickly titrate down and use the lowest possible FiO_2 to maintain a PaO_2 of 50 to 60 or higher (or saturation >90%) to avoid oxygen toxicity (theoretically, FiO_2 <60% is usually safe).
   b. PEEP is positive pressure maintained at the end of a passive exhalation to keep alveoli open. 5 cm H_2O is an appropriate initial setting. High levels of PEEP increase the risk of barotrauma (injury to airway = pneumothorax) and decrease cardiac output (decreased venous return from increased intrathoracic pressure).

CLINICAL PEARL 2-11

Parameters to Consider in Extubation or Weaning From the Ventilator: The More Criteria That Are Met, the More Likely That Extubation Will Be Tolerated

- Whether patient has an adequate respiratory drive and is hemodynamically stable
- Intact cough (when suctioning secretions)
- PaO_2/FiO_2 >200, $PaCO_2$ <45
- O_2 saturation of >90%, PEEP of ≤5 cm H_2O, FiO_2 <40%, RR <35 breaths/min, minute ventilation ≤12 L/min, vital capacity >10 mL/kg
- Rapid shallow breathing index (RSBI, RR divided by tidal volume) <105
- Negative inspiratory pressure <−20 cm H_2O or more negative

Quick HIT

The presence of an ET tube does not prevent aspiration from occurring.

D. Complications

1. Anxiety, agitation, discomfort
   a. Both sedation and analgesia are important; paralytics should be used during intubation and can be used after intubation if the patient continues to be agitated or experiences too much patient–ventilator asynchrony. Always ensure adequate sedation before paralysis
2. Difficulty with tracheal secretions—suction on a regular basis
3. Ventilator-associated pneumonia (risk is ∼1% per day).
4. Barotrauma—caused by high airway pressures
5. **Tracheomalacia** (softening of the tracheal cartilage)—due to the prolonged presence of an endotracheal tube (ETT)
6. Laryngeal damage during intubation
7. Gastrointestinal effects (stress ulcers and cholestasis)—increased risk in mechanically ventilated patients. Patients who are mechanically ventilated for >48 hours should be on a proton pump inhibitor (PPI) or H2 blocker

Quick HIT

When a patient is ventilator dependent for 2 or more weeks, a tracheostomy is usually performed to prevent tracheomalacia.

Diseases of the Pulmonary Vasculature

Pulmonary Hypertension

A. General Characteristics

1. Defined as a mean pulmonary arterial pressure greater than 20 mm Hg at rest
2. There are multiple pathophysiologic processes that can cause pulmonary HTN (Clinical Pearl 2-12):
   a. Passive due to resistance in the pulmonary venous system (e.g., left heart failure, mitral stenosis, atrial myxoma)
   b. Hyperkinetic (left-to-right cardiac shunts such as atrial septal defect or patent ductus arteriosus)
   c. Obstruction (e.g., PE, pulmonary artery stenosis)
   d. Pulmonary vascular obliteration (e.g., collagen vascular diseases)
   e. Pulmonary vasoconstriction (e.g., chronic hypoxemia, COPD, obstructive sleep apnea [OSA])
3. Classification of pulmonary HTN is based on the revised WHO classification system:
   a. Group 1: Pulmonary arterial HTN (PAH)
      - Idiopathic, familial, veno-occlusive disease, and PAH with associated conditions (connective tissue disorders, congenital shunting, HIV, drugs and toxins).
      - An abnormal increase in pulmonary arteriolar resistance leads to thickening of pulmonary arteriolar walls. This worsens the pulmonary HTN, which in turn causes further wall thickening, thus leading to a vicious cycle.
      - The cause is unknown; it usually affects young or middle-aged women.
      - The prognosis is poor. Mean survival is 2 to 3 years from the time of diagnosis.
   b. Group 2: Left heart disease
      - Secondary to any cause of left heart failure, including valvular disease
   c. Group 3: Lung disease and/or chronic hypoxemia

- Causes include ILD, COPD, OSA, and any other cause of chronic hypoxemia

d. Group 4: Chronic thromboembolic disease
- Recurrent PE (many patients do not have symptoms of PE), including nonthrombotic etiologies (e.g., tumor emboli)

e. Group 5: Miscellaneous
- Pulmonary vascular compression (e.g., tumors or lymphadenopathy), sarcoidosis, PLCH, etc.

CLINICAL PEARL 2-12

How to Determine the Cause of Pulmonary HTN

- Perform a series of tests (CXR, PFTs, ABGs, serology, echocardiogram, cardiac catheterization). These tests will give you enough information to recognize heart disease or lung disease as the cause of pulmonary HTN.
- If the cause is not revealed (neither heart nor lung), then obtain a V/Q scan: this indicates either PE or primary pulmonary hypertension (pulmonary arterial hypertension, PAH). Note that PAH is a diagnosis of exclusion.

B. Clinical Features

1. Symptoms
   a. Dyspnea on exertion
   b. Fatigue
   c. Chest pain—exertional
   d. Syncope—exertional (with severe disease)
   e. Weight gain from edema
2. Signs
   a. Loud pulmonic component of the second heart sound (P_2) and subtle lift of sternum (sign of RV dilatation)—**these may be the only findings, and yet the patient may still have a devastating disease!**
   b. When right ventricular failure occurs, the corresponding signs and symptoms appear (JVD, hepatomegaly, ascites, peripheral edema).

C. Diagnosis

1. ECG: often suggests right ventricular hypertrophy—specifically, right-axis deviation and right atrial abnormality are frequently present
2. CXR: enlarged pulmonary arteries with or without clear lung fields based on the cause of pulmonary hypertension
3. Echocardiogram: elevated pulmonary artery systolic pressure is **suggestive** of pulmonary HTN.
   a. Dilated pulmonary artery
   b. Dilatation/hypertrophy of RA and RV
   c. Abnormal movement of IV septum (due to increased right ventricular volume)
4. Right heart catheterization: required for **confirming** diagnosis of pulmonary HTN. Reveals increased mean pulmonary artery pressure >20 mm Hg

D. Treatment

1. One specific treatment plan cannot be recommended due to the variety of causes of pulmonary HTN. If the pulmonary HTN is secondary to another disease process (e.g., recurrent PE), then the underlying disease should be treated and optimized.
2. Vasoactive agents are typically used in PAH (Group 1), since trials have been done in this group.
   a. Right heart catheterization with a trial of vasodilators should precede the use of these agents.
   b. Vasoactive agents may lower pulmonary vascular resistance in some patients. Available options include inhaled nitric oxide, phosphodiesterase inhibitors (e.g., sildenafil), guanylate cyclase stimulants (e.g., riociguat), oral CCBs, prostacyclins (e.g., epoprostenol), and endothelin receptor antagonists (e.g., bosentan).
3. Many patients require home oxygen, diuretics, and occasionally inotropes (e.g., digoxin).
4. Lung transplantation in qualified patients.

Quick HIT

Cor pulmonale is best thought of as the right-sided counterpart to left ventricular heart disease due to systemic HTN.

Cor Pulmonale

A. General Characteristics

1. Cor pulmonale is defined as right ventricular hypertrophy with eventual RV failure resulting from pulmonary HTN, **secondary to pulmonary disease.**
2. The definition does not encompass any of the causes of pulmonary HTN due to left-sided heart disease (such as mitral stenosis or left-to-right shunts).

Quick HIT

Death due to cor pulmonale: Many COPD patients die of right ventricular failure secondary to chronic pulmonary HTN. Many deaths due to PE result from acute pulmonary HTN and right ventricular failure.

B. Causes

1. It is most commonly secondary to COPD.
2. Other causes include recurrent PE, ILD, asthma, CF, and OSA.

C. Clinical Features

1. Decrease in exercise tolerance
2. Cyanosis and digital clubbing
3. Signs of right ventricular failure: hepatomegaly, edema, JVD
4. Parasternal lift

D. Diagnosis

1. CXR: enlargement of the RA, RV, and pulmonary arteries

2. ECG: right-axis deviation, P pulmonale (peaked P waves), right ventricular hypertrophy
3. Echocardiogram: right ventricular dilatation, but normal LV size and function; useful in excluding LV dysfunction

***Quick* HIT**

Other sources of emboli to the lungs:
- Fat embolism (long-bone fractures)
- Amniotic fluid embolism (during or after delivery)
- Air embolism (trauma to thorax, indwelling venous/arterial lines)
- Septic embolism (IV drug use)
- Schistosomiasis

E. Treatment

1. Treat the underlying pulmonary disorder.
2. Use diuretic therapy cautiously because patients may be preload dependent.
3. Apply continuous long-term oxygen therapy if the patient is hypoxic.
4. Administer digoxin only if there is coexistent LV failure.
5. A variety of vasodilators have been studied; no definite improvement has been shown with their use.

***Quick* HIT**

If a patient with long-bone fracture develops dyspnea, mental status change, and petechiae, think **fat embolism**. Respiratory failure and death can ensue rapidly.

Pulmonary Embolism

A. General Characteristics

1. A PE occurs when a thrombus in another region of the body embolizes to the pulmonary vascular tree via the RV and pulmonary artery. Blood flow distal to the embolus is obstructed.

2. Consider PE and deep venous thrombosis (DVT) as a continuum of one clinical entity (venous thromboembolism or VTE)—diagnosing either PE or DVT is an indication for treatment.
3. Sources of emboli
   a. Lower extremity DVT—PE is the major complication of DVT.
      - Most pulmonary emboli arise from thromboses in the deep veins of lower extremities above the knee (iliofemoral DVT).
      - Pulmonary emboli can also arise from the deep veins of the pelvis.
      - Although calf vein thrombi rarely embolize to the lungs, one-third of these thrombi can progress into the proximal veins, increasing the risk of PE.
   b. Upper extremity DVT is a rare source of emboli (it may be seen in IV drug use).
4. Risk factors are those for DVT (see Clinical Pearl 2-13)
5. Pathophysiology
   a. Emboli block a portion of pulmonary vasculature, leading to increased pulmonary vascular resistance, pulmonary artery pressure, and right ventricular pressure. If it is severe (large blockage), acute cor pulmonale may result.
   b. Blood flow decreases in some areas of the lung. Dead space is created in areas of the lung in which there is ventilation but no perfusion. The resulting hypoxemia and hypercarbia drive respiratory effort, which leads to tachypnea.
   c. If the size of the dead space is large (large PE), clinical signs are more overt (SOB, tachypnea).
6. Course and prognosis
   a. Most often, PE is clinically silent. **Recurrences are common,** which can lead to development of chronic pulmonary HTN and chronic cor pulmonale.
   b. When PE is undiagnosed, mortality approaches 30%. A significant number of cases are undiagnosed (as many as 50%).
   c. When PE is diagnosed, mortality is 10% in the first 60 minutes. **Of those who survive the initial event, approximately 30% of patients will die of a recurrent PE, if left untreated. Most deaths are due to recurrent PE within the first few hours of the initial**

PE. Treatment with anticoagulants decreases the mortality to 2% to 8%.

Quick HIT

Complications in patients with PE who survive the initial event include the following:

- Recurrent PE
- Pulmonary HTN (up to 5% of patients)

Quick HIT

Two important studies to know:

1. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) is a landmark study (JAMA 1990;263:2753). Guides treatment, if V/Q is performed.
2. The Christopher Study (JAMA 2006;295:72–179). Guides treatment, if spiral CT is performed.

CLINICAL PEARL 2-13

Risk Factors for DVT/PE

- Age >60 years
- Malignancy
- Prior history of DVT, PE
- Hereditary hypercoagulable states (factor V Leiden, protein C and S deficiency, antithrombin III deficiency)
- Prolonged immobilization or bed rest, long-distance travel
- Cardiac disease, especially CHF
- Obesity
- Nephrotic syndrome
- Major surgery, especially pelvic surgery (orthopedic procedures)
- Major trauma
- Pregnancy, estrogen use (oral contraceptives)

B. Clinical Features

1. Symptoms (frequency per the PIOPED study)
   a. Dyspnea (73%)
   b. Pleuritic chest pain (66%)
   c. Cough (37%)
   d. Orthopnea (28%)
   e. Wheezing (21%)
   f. Hemoptysis (13%)
   g. Note that only one-third of patients with PE will have signs and symptoms of a DVT
   h. Syncope may be seen in massive PE
2. Signs (frequency per the PIOPED study)
   a. Tachypnea (54%)
   b. Tachycardia (24%)
   c. Rales (18%)
   d. Decreased breath sounds (17%)
   e. Increased P2 (23%)
   f. Jugular venous distension (14%)
   g. Shock with rapid circulatory collapse in massive PE

Quick HIT

Signs and symptoms are nonspecific and not reliable indicators for the presence of PE. This often leads to delay in diagnosis and treatment. Utilize risk calculators to assess pretest probability for PE when suspecting this diagnosis.

C. Diagnosis

1. ABG levels are not diagnostic for PE (see Clinical Pearl 2-14)
   a. PaO_2 and $PaCO_2$ are low (the latter due to hyperventilation) and pH is high; thus, there is typically a respiratory alkalosis.
   b. The A–a gradient is usually elevated. A normal A–a gradient makes PE less likely, but cannot be relied on to exclude the diagnosis.
2. CXR—usually normal
   a. Atelectasis or pleural effusion may be present.
   b. The main usefulness is in excluding alternative diagnoses.

c. Classic radiographic signs, such as *Hampton hump* or *Westermark sign,* are rarely present.

3. CT pulmonary angiography (CTPA)
   a. **Diagnostic test of choice.**
   b. Has been found to have good sensitivity (>90%) and specificity.
   c. Can visualize very small clots (as small as 2 mm); may miss clots in small subsegmental vessels (far periphery).
   d. The test of choice in most medical centers.
   e. In combination with clinical suspicion, guides treatment (see Figure 2-16).
   f. CTA may be relatively contraindicated in patients with a moderate to severe contrast allergy or renal insufficiency (eGFR <30 mL/min per 1.73 m^2). Weigh these risks with benefit of performing a CTPA.

CLINICAL PEARL 2-14

Workup of PE

It is often difficult to definitively diagnose or rule out PE. The following tests provide an adequate basis for treating PE with anticoagulation:

- Intraluminal filling defects in central, segmental, or lobular pulmonary arteries on CTA
- DVT diagnosed with ultrasound and clinical suspicion
- V/Q scan with high probability PE and high clinical suspicion
- Positive pulmonary angiogram (rarely done)

The following can essentially rule out PE:

- Low-probability V/Q scan (*or* normal helical scan) **and** low clinical suspicion
- Negative pulmonary angiogram (definite)
- Negative D-dimer assay **and** low clinical suspicion

Adapted from PIOPED data. *JAMA.* 1990;263:2753.

Quick HIT

If CTA is negative for PE, and clinical probability of PE is high, there is a 5% incidence of PE. So negative results should be interpreted with caution, if the patient has a high clinical probability of PE.

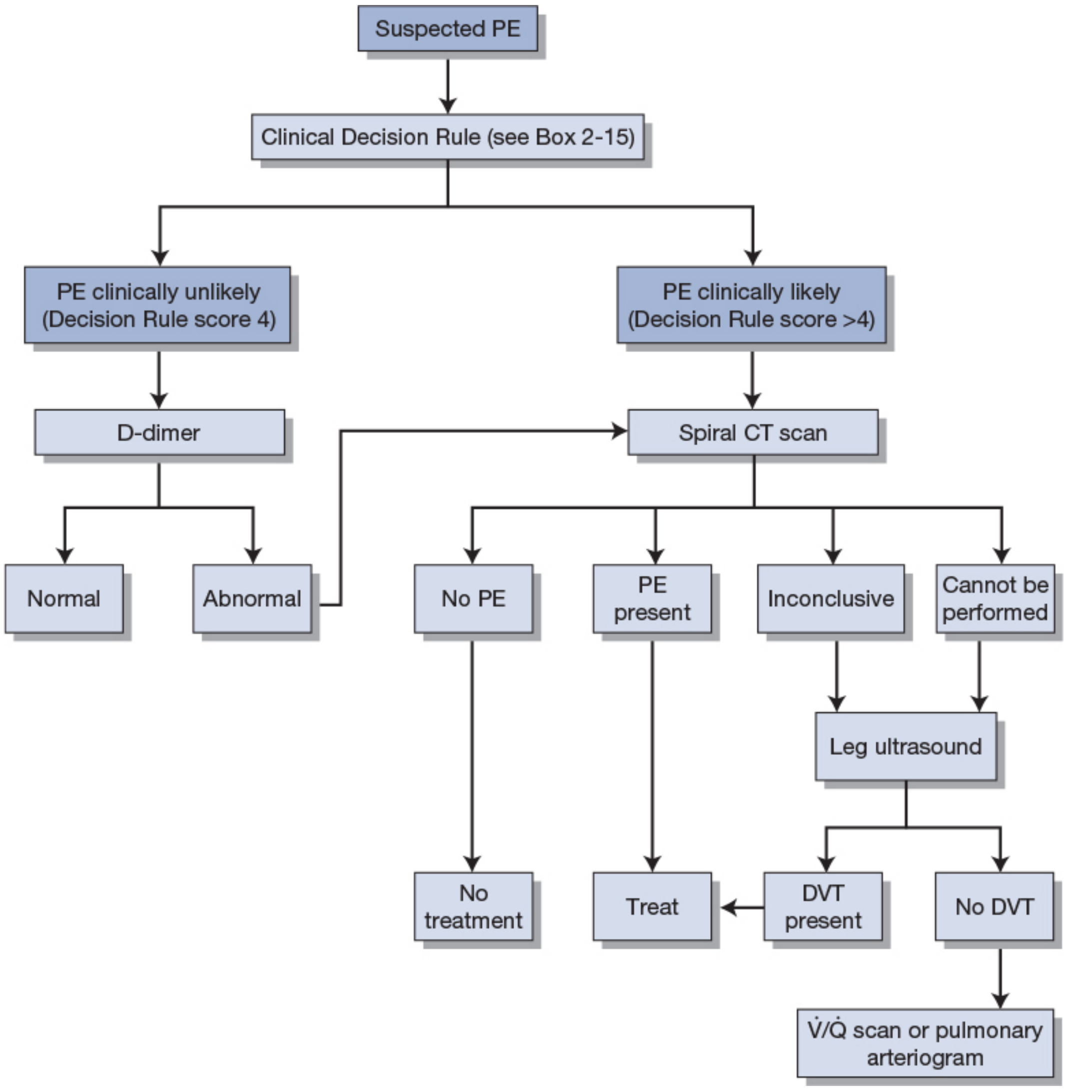


FIGURE 2-16 **Workup in a patient with suspected pulmonary embolism.**

4. D-dimer assay
   a. D-dimer is a specific fibrin degradation product; levels can be elevated in patients with PE and DVT.
   b. D-dimer assay is a fairly sensitive test (90% to 98%). **If results are normal <u>and</u> pretest probability for PE is low,** PE is very unlikely.
   c. Specificity is low—D-dimer is an acute phase reactant, so it can be elevated in any inflammatory state (MI, infection, postoperative, etc.). Any cause of clot or increased bleeding can also elevate the D-dimer level.
5. V/Q (ventilation–perfusion lung) scan

a. Reserved for cases in whom CTPA is contraindicated or inconclusive.
   - Most useful when the CXR is clear and when there is no underlying cardiopulmonary disease.

b. Interpretation of results: can be either normal, low probability, intermediate probability, or high probability (treatment guidelines based on PIOPED study).
   - Most scans are indeterminate, which is the major limitation of V/Q scans.
   - Interpretation of V/Q scan requires combining results of V/Q scan with clinical pretest probability.
   - A high-probability V/Q scan with high clinical pretest probability has a very high sensitivity for PE; treat with anticoagulation.
   - **If the V/Q scan shows low or intermediate probability, clinical suspicion determines the next step.** If clinical pretest probability is high, consider empiric anticoagulation or further testing (CTPA, venous duplex ultrasound, pulmonary angiography) after risks/benefits discussion. If pretest probability is low, and V/Q scan shows low-probability scan, PE is unlikely (<4% chance of having PE).

6. Venous duplex ultrasound of the lower extremities
   a. Used mostly for patients in whom PE is suspected but definitive imaging (CTPA or V/Q scan) is contraindicated or indeterminate.
   b. If there is a positive result, treat with anticoagulation (core tenets of DVT/PE management are similar).
   c. This test is helpful when positive, but of **little value when negative** (negative results occur in 50% of patients with proven PE; a normal ultrasound does not rule out PE).

7. Catheter-based pulmonary angiography
   a. Historical gold standard for diagnosis of PE. Now infrequently used due to its invasive nature. Contrast injected into the pulmonary artery branch after percutaneous catheterization of the femoral vein.
   b. Consider when noninvasive testing is equivocal and risk of anticoagulation is high, or if the patient is hemodynamically unstable and embolectomy may be required. Angiography is rarely performed because it carries a 0.5% mortality.

8. **Overall, the workup of suspected PE is based on clinical pretest probability**. The Wells criteria (Clinical Pearl 2-15) is a scoring system that takes this into account and helps guide the workup. The PE rule-out criteria (PERC rule) can also be used to identify patients at low pretest probability for PE.
   a. If low pretest probability for PE based on the scoring system, then the pretest probability for PE is low and a normal D-dimer can exclude PE.
   b. If high pretest probability for PE, a D-dimer should not be used, as results can be falsely normal. CTPA should be performed given its high sensitivity and specificity.

Quick HIT

If pretest probability of PE is low, D-dimer test is a noninvasive test that can be used to rule out PE. So if D-dimer is negative, you can rule out a clot. D-dimer is not helpful when pretest probability of PE is high.

CLINICAL PEARL 2-15

Dichotomized Clinical Decision Rule for Suspected Acute Pulmonary Embolism (Modified Wells Criteria)

Factor	Points
Symptoms and signs of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100 beats/min	1.5
Immobilization (>3 days) or surgery in previous 4 wks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy (current therapy, or in previous 6 months, or palliative)	1.0

Score ≤4 indicates that PE is unlikely, score >4 indicates that PE is likely.

Adapted with permission from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83(3):416–420. Copyright © Georg Thieme Verlag KG.

Quick HIT

Start therapeutic heparin as initial treatment. Also start warfarin at the same time. Goal is therapeutic INR of 2 to 3.

A 28-year-old woman with a history of asthma presents to the Emergency Department complaining of an "asthma attack." She regularly uses inhaled albuterol and fluticasone, but is experiencing worsening shortness of breath for the past hour and is not responding to the albuterol inhaler. She broke her tibia in a skiing accident 1 week ago and an open reduction with internal fixation was performed. She takes oral contraceptive pills but denies using any other medications. On examination, her heart rate is 115 beats/min, her respiratory rate is 28 breaths/min, and her oxygen saturation is 94%. There are no murmurs or abnormal lung sounds. There is a cast on her right lower leg, and the right thigh above the cast is swollen and erythematous compared to the left thigh.

Which of the following is the most likely diagnosis?

A. Pulmonary embolism
B. Fat embolism
C. Acute asthma exacerbation
D. Bacterial pneumonia

- **The answer is A: Pulmonary embolism.** Despite the fact that the patient has asthma and claims to be having an exacerbation, there is no significant wheezing on examination, suggesting an alternative diagnosis. The patient has several risk factors for pulmonary embolism, meeting the three categories of Virchow triad of thrombosis: stasis (likely has some degree of inactivity from her fractured tibia), endothelial injury (fractured tibia and orthopedic surgery), and a hypercoagulable state (oral contraceptive pills). A CT angiogram would be the appropriate next step in diagnosis, and she should receive empiric anticoagulation. **(B)** Fat embolism can occur as a result of a long bone fracture; however, this usually occurs within days of the trauma. Fat emboli syndrome is a distinct entity and presents with dyspnea, neurologic findings, and a petechial rash. **(C)** As mentioned previously, this patient has a history of asthma but

you should avoid the temptation to explain her current symptoms with that diagnosis. **(D)** Though a bacterial pneumonia is possible, it is less likely based on the information provided in the vignette.

Quick HIT

Why PE and DVT are problematic for physicians:
- Clinical findings are sometimes subtle in both.
- Noninvasive imaging tests do not always detect either condition.
- Anticoagulation carries significant risk and should always be weighed against bleeding risk.

D. Treatment

1. Assess hemodynamic stability. If hypotensive, this is considered a high-risk or "massive" PE. These patients should be admitted to the intensive care unit and undergo aggressive fluid resuscitation and/or vasopressor support. Anticoagulation with unfractionated heparin is recommended. Thrombolysis should be considered with help of multidisciplinary team (radiology, pulmonary, cardiology).
2. Supplemental oxygen to correct hypoxemia. Severe hypoxemia or respiratory failure requires intubation and mechanical ventilation.
3. Start anticoagulation therapy depending on clinical suspicion for PE and bleeding risk. Prevents further clot formation, but does not lyse existing emboli or diminish thrombus size.
   a. Start immediately if clinical suspicion is high. Decision to anticoagulate is individual and must take into account patient's bleeding risk. **Do not wait for studies to confirm PE if clinical suspicion is high.**
4. Select anticoagulation agent based on patient factors (e.g., bleeding risk, active cancer, pregnancy, renal function, cost, need for reversal agent, preferred route of administration, etc.).
   a. Direct oral anticoagulant (DOAC): For many patients, a DOAC (rivaroxaban or apixaban) is a good option. If using rivaroxaban or apixaban, concurrent treatment with heparin during initiation is not necessary as these medications are effective immediately. Other

DOACs (edoxaban, dabigatran) require dual therapy with heparin for initiation.

b. Warfarin: less often used compared with DOACs as it requires INR monitoring and is difficult to maintain in therapeutic range. Target INR range is 2 to 3 for treatment of PE/DVT. Requires concurrent administration with heparin for initiation.
c. Low–molecular-weight heparin (LMWH): subcutaneous injection. Option for patients in whom oral anticoagulation is less ideal (malabsorption, inability to take oral medications, prohibitive cost of other options).
d. Unfractionated heparin (UFH): IV infusion, can only be given inpatient and requires frequent monitoring. Preferred for hemodynamically unstable PE, or if anticipating need for rapid discontinuation or reversal (e.g., upcoming procedure or high bleeding risk). Eventually requires transition to an agent above.
e. Duration: continue anticoagulation for 3 to 6 months or more, depending on risk factors. Some patients at significant risk for recurrent PE (e.g., unprovoked clot in absence of risk factors, malignancy, hypercoagulable state) may be considered for lifelong anticoagulation.

5. Thrombolytic therapy—for example, streptokinase, tPA
   a. Speeds up the lysis of clots.
   b. Thrombolysis can lead to early hemodynamic improvement (with unclear mortality benefit) at the cost of major bleeding. Therefore, its use is often on a case-by-case basis.
   c. Situations in which thrombolysis should be considered:
      - Patients with high-risk PE who are hemodynamically unstable (persistent hypotension).
      - Patients with intermediate-risk PE with evidence of right heart dysfunction (elevated BNP or troponin).
   d. Catheter-directed thrombolysis has lower systemic side effects and should be considered in patients at high risk for systemic fibrinolysis or surgery.
6. Inferior vena cava (IVC) filter placement
   a. Used primarily in patients with acute DVT and PE who have an absolute contraindication to anticoagulation (e.g., active bleeding, recent surgery, hemorrhagic stroke, etc.). Also used sometimes in

combination with anticoagulation for patients who may not tolerate another embolic event (poor cardiopulmonary reserve).

b. Once bleeding risk is sufficiently low, start anticoagulation and remove IVC filter, when able (retrieval rates are low).

c. Complications of IVC filter placement: filter migration or misplacement, filter erosion and perforation of IVC wall, and IVC obstruction due to filter thrombosis.

7. Surgical or catheter-directed thrombectomy

   a. Consider in patients with hemodynamic instability, a large, proximal thrombus, and who are poor candidates for thrombolysis.

   b. Emboli can be removed surgically or with a catheter.

Quick HIT

- INR is a way of reporting the PT in a standardized fashion.
- Warfarin increases INR values.
- “Therapeutic” INR is usually between 2 and 3. Notable exceptions are certain prosthetic mechanical heart valves and treatment of antiphospholipid antibody syndrome, for which a higher target INR may be recommended.

Quick HIT

If anticoagulation is contraindicated in a patient with a DVT or PE, an IVC filter is indicated. Once that contraindication has resolved, the IVC filter should be removed and patient should be anticoagulated.

Miscellaneous Topics

Pulmonary Aspiration

A. General Characteristics

1. Pulmonary aspiration syndromes can be due to different types of aspirates.

a. Acidic gastric contents, which are especially damaging to the lungs.
b. Aspiration of oropharyngeal flora, which can lead to infection.
c. Foreign body/fluids (e.g., chemicals).

2. **The right lung is most often involved due to anatomy** (right main bronchus follows a straighter path downward), **particularly the lower segments of the right upper lobe and the upper segments of the right lower lobe.**
3. Predisposing factors
   a. Reduced level of consciousness (e.g., seizures, stroke, sedating drugs)
   b. Alcohol use disorder
   c. Advanced age
   d. Extubation (impaired pharyngeal or laryngeal function)
   e. Excessive vomiting, ileus
   f. Tube feeding, tracheostomy tubes
   g. Anesthesia/surgery
   h. Neuromuscular diseases
   i. Esophageal disorders (e.g., achalasia, gastroesophageal reflux disease [GERD], cancer)

Quick HIT

Aspiration pneumonia can be difficult to distinguish from aspiration pneumonitis. Patients with aspiration pneumonia will have clinical signs of pneumonia (dyspnea, hypoxia, cough, fever, etc.). Organisms are often mixed (aerobic–anaerobic).

B. Clinical Features

1. Presentation is variable. Some patients develop acute onset of respiratory distress. However, most often, the patient appears well, but later develops respiratory dysfunction (cough, SOB, fever, tachypnea, hypoxemia, or frothy sputum).
2. Aspiration event may be unwitnessed, with development of acute respiratory failure with no obvious trigger.
3. Fever may or may not be present.

C. Diagnosis

1. Findings on CXR are variable and resemble infiltrates that mimic bacterial pneumonia. Atelectasis and local areas of collapse may also be present.
2. Differentiating between aspiration pneumonitis and aspiration pneumonia can be difficult. Aspiration pneumonitis may show early infiltrates on CXR, whereas aspiration pneumonia takes a few days to develop. Decision of whether to treat with empiric antibiotics depends on whether clinical signs of pneumonia are present. Aspiration pneumonitis will often spontaneously resolve without antibiotics.

D. Treatment

1. If aspiration was witnessed: ABCs (airway, breathing, and circulation), supplemental oxygen, and supportive measures.
2. If aspiration pneumonia is suspected, give antibiotics based on care setting. Addition of anaerobic coverage is recommended if strong clinical history of bacterial aspiration (such as dysphagia, altered mental status, and severe periodontal disease). For community-acquired pneumonia (CAP), treat with ampicillin-sulbactam or amoxicillin-clavulanate. For hospital-acquired pneumonia or for severely ill patients, piperacillin-tazobactam, imipenem, or meropenem are appropriate. Need for coverage of methicillin-resistant *S. aureus* with vancomycin is determined based on specific risk factors.
3. If airway obstruction is present, early bronchoscopy is indicated.
4. Prevention is critical in patients at high risk for aspiration: Keep the head of the bed elevated. Nasogastric tubes and enteral feeding have not been shown to decrease the risk of aspiration.

Quick HIT

Aspiration can lead to lung abscess if untreated. Poor oral hygiene predisposes to such infections. Foul-smelling sputum may indicate anaerobic infection.

Dyspnea

A. General Characteristics

1. Distinguish acute from chronic dyspnea.
2. Patients with chronic dyspnea usually have either heart or lung disease or both. It may be difficult to distinguish between the two.
3. Acute dyspnea has a broad differential, but common causes are MI, heart failure, cardiac tamponade, bronchospasm, PE, pneumothorax, pneumonia, or upper airway obstruction.
4. The most common causes of chronic dyspnea are asthma, COPD, ILD, heart disease, and obesity or physical deconditioning.
5. Assess the patient's baseline level of activity, whether the dyspnea is new in onset, triggers (including exertion or positional changes), associated symptoms, and temporal progression of symptoms.
6. If the patient has a history of smoking, cough, sputum, repeated infections, or occupational exposure, lung disease is likely to be the reason for chronic dyspnea.

Quick HIT

Depending on patient presentation, any of the following tests may be helpful in distinguishing between lung and heart disease:

- CXR
- Sputum Gram stain and culture (if patient has sputum)
- PFTs
- ABGs
- BNP
- ECG, echocardiogram

B. Causes

1. Cardiovascular causes
   a. Heart failure
   b. Ischemic heart disease, acute myocardial infarction
   c. Pericarditis, cardiac tamponade
   d. Arrhythmias
   e. Valvular disease
   f. Congenital heart disease

2. Pulmonary causes
   a. Obstructive lung diseases—COPD, asthma, bronchiectasis
   b. PE
   c. ARDS
   d. Pneumonia, TB, bronchitis
   e. Pleural effusion, pulmonary edema
   f. Pneumothorax
   g. Upper airway obstruction, foreign body aspiration, anaphylaxis
   h. ILD
   i. Chest wall abnormalities (kyphoscoliosis), rib fracture
3. Psychiatric disease—generalized anxiety disorder, panic attacks, hyperventilation (first exclude other organic causes of dyspnea)
4. Systemic causes—severe chronic anemia, sepsis, metabolic acidosis (DKA), GERD, medication (salicylate overdose), methemoglobinemia
5. Chest wall abnormalities—kyphoscoliosis, rib fracture, ankylosing spondylitis
6. Neuromuscular diseases that weaken respiratory muscles—myasthenia gravis, muscular dystrophy

Quick HIT

Patients with chronic COPD can also experience paroxysmal nocturnal dyspnea. Excessive airway secretions can accumulate at night causing airway obstruction, resulting in dyspnea that awakens the patient and forces them to clear the airway. Therefore, paroxysmal nocturnal dyspnea is not specific to heart disease.

C. Diagnosis

1. Thorough history and physical examination, vital signs.
2. Pulse oximetry—normal is 96% to 100% on room air. Be aware that the baseline oxygen saturation of many COPD patients is chronically low.
3. ABG—may be indicated if oxygen saturation is low on pulse oximetry, if hypercarbia is suspected, or to evaluate for acid–base abnormalities.
4. CXR—can reveal pneumothorax, pleural effusion, pulmonary vascular congestion secondary to CHF, infiltrates due to pneumonia, ILD, and so on.

5. CBC—to evaluate for anemia, infection.
6. BNP—to evaluate for signs of fluid overload.
7. ECG—may show ventricular hypertrophy or evidence of ischemic heart disease.
8. Echocardiogram—for further evaluation of CHF, valvular heart disease.
9. PFTs—perform if all of the above are normal or if obstructive lung disease is suspected. See Table 2-7.
10. V/Q scan or CTPA scan—perform if PE is suspected.
11. Bronchoscopy—indicated if foreign body aspiration is suspected.

Quick HIT

A chronic CO_2 retainer (common in COPD patients) usually has normal pH and increased HCO_3 levels. If CO_2 retention is acute, pH will be decreased and HCO_3 will be closer to normal levels.

D. Treatment

1. Treat the underlying cause.
2. Administer supplemental oxygen as needed (see Table 2-6).
3. Use intubation and mechanical ventilation in the following situations:
   a. If impending respiratory failure is suspected
   b. If patient is unable to protect airway (e.g., decreased mental status, stroke, drug overdose)
   c. Severe hypoxia despite supplemental oxygen (PaO_2 <50 to 60)
   d. Severe hypercarbia ($PaCO_2$ >50)
4. Exercise and conditioning may improve perception of dyspnea.

Quick HIT

Massive Hemoptysis

- Defined as more than 150 mL of blood in 24 hours, although different amounts may be life-threatening depending on patient's cardiopulmonary reserve.
- Airway protection is key. Intubate if necessary.
- Position the patient so suspected bleeding site is in dependent position (e.g., if right lung is bleeding, position patient in right decubitus position).
- Bronchoscopy can help identify the bleeding source.
- Use bronchial artery embolization or balloon tamponade of the airway if indicated.

Hemoptysis

A. General Characteristics

1. Defined as expectoration of blood; hemoptysis varies widely in severity and medical significance. The amount of blood does not necessarily correspond with the severity of the underlying cause.
2. Differential diagnosis
   a. Most common causes include:
      - Bronchitis and bronchiectasis (50% of cases)
      - Lung cancer (bronchogenic carcinoma)
      - TB/fungal infections
      - Pneumonia
      - Often the etiology remains idiopathic after thorough evaluation (up to 30% of cases)

   b. Other causes include:
      - Goodpasture syndrome (anti-GBM antibody disease)
      - PE with pulmonary infarction
      - Aspergilloma within cavities
      - Mitral stenosis (elevated pulmonary venous pressure)
      - Hemophilia

TABLE 2-7 Important Pulmonary Studies

Test	Explanation of Test	Use	Comments
Pulse oximetry	• Measures percentage of oxygenated hemoglobin. • Follows a sigmoid curve in relationship to partial pressure of oxygen (PaO_2) in the arterial blood. • Oxygen saturation of ≤88% is the established criterion for receiving home oxygen.	• Useful in most categories of patients in whom pulmonary disease is suspected. • Also helpful in assessing a patient with dyspnea, whether acute or chronic.	• Useful as a screening test because it is very sensitive for detecting gas exchange abnormalities. • Not very specific. • Sensitivity is increased during exercise. • Can underestimate degree of hypoxemia in patients with darker skin tones (racial bias).
Arterial blood gas (ABG)	Measures the partial pressures of oxygen and carbon dioxide as well as the pH of the arterial blood. • Normal pH: 7.35–7.45 • Normal PaO_2: decreases with age (90 is normal in a 20-yr-old person) • Normal $PaCO_2$: 35–45 mm Hg	For every 10 mm Hg increase or decrease in $PaCO_2$, there should be a corresponding increase or decrease in pH by 0.08. In general, if the change in pH is in the same direction as change in $PaCO_2$, then the primary disorder is metabolic. When there is an inverse relationship, the primary disorder is respiratory.	• ABG is not necessary in all patients with pulmonary dysfunction. Ask yourself whether the results of the ABG are going to influence what you do for the patient before performing it. • ABG is painful, and radial artery spasm can result in ischemia of the hand in patients with radial-dominant circulation.
Spirometry	• From maximum inspiration, the patient exhales as rapidly and forcibly as possible to	• Helps to distinguish obstructive from restrictive lung disease. • Useful in assessing degree of functional impairment as well as	• Volumes are measured as percentages of predicted values based on age, height, and sex.

	maximum expiration. • Spirometer plots the change in lung volume against time (see lung volumes below).	monitoring effectiveness of treatment (e.g., during asthma exacerbation). • May detect respiratory impairment in asymptomatic patients (e.g., smokers).	• Incorrect measurement or technique may lead to false positives. • There are race-based correction factors for lung volumes, which are not based on actual physiology (racial bias, can lead to misclassification of severity of a patient's lung disease)
DL_{CO}	• The patient breathes in a small, specific amount of CO, and the amount transferred from alveolar air to pulmonary–capillary blood is measured. • CO is a diffusion-limited gas, so other variables are eliminated. • Essentially measures the surface area of the alveolar–capillary membrane.	• Can often distinguish between asthma, emphysema, and COPD. • Useful in monitoring various conditions, such as sarcoidosis and emphysema.	1. Causes for low DL_{CO} include: • Emphysema • Sarcoidosis • Interstitial fibrosis • Pulmonary vascular disease • Also, lower with anemia due to reduced binding of CO to hemoglobin 2. Causes for high DL_{CO}: • Asthma (increased pulmonary–capillary blood volume) • Obesity • Intracardiac left-to-right shunt • Exercise • Pulmonary hemorrhage (alveolar RBCs bind with CO)
Ventilation–perfusion (V/Q) scan	• Compares the degree of ventilation to perfusion of the lungs; an exact match would	Diagnosis of PE	It is very rare to have a "normal" or "negative" V/Q scan. When V/Q scans are ordered for evaluation of suspected PE, the result is usually "low,"

	correspond to a V/Q ratio of 1. • A high V/Q ratio occurs when there is inadequate perfusion of an adequately ventilated lung. Thus, dead space is increased. • The normal ratio of ventilation to perfusion is 0.8; so there is normally some degree of V/Q mismatch, with some degree of shunting.		"indeterminate," or "high probability."
Methacholine challenge	Assesses degree of airway hyperreactivity.	Patients in whom asthma or COPD is suspected.	Sensitive in detecting airway hyperresponsiveness in mild asthma.

B. Diagnosis

1. Verify that hemoptysis has truly occurred. For example, superficial mouth lacerations, epistaxis, or hematemesis may be confused with hemoptysis.
2. History and physical
   a. Fever, night sweats, and weight loss suggest TB.
   b. Fevers and chills or a history of HIV suggests either pneumonia or TB.
   c. Look for risk factors for PE.
   d. In the presence of acute renal failure or hematuria, anti-GBM or Goodpasture syndrome should be considered.
3. Diagnostic studies
   a. CXR
      - May be a clear indicator of a pathogenic process or even diagnostic—for example, if fungus ball, irregular mass,

granuloma, or opacity consistent with pulmonary infarction is present.
    - A normal CXR does not exclude a serious condition, especially PE or lung cancer.
  b. Fiberoptic bronchoscopy
    - Should be performed even if CXR is normal and if there is a significant clinical suspicion for lung carcinoma.
    - Look for a small tumor that may not be evident on a radiograph.
    - May localize the site of bleeding.
4. CT of chest—performed as a complement to bronchoscopy or as a substitute if there are contraindications to bronchoscopy.

Quick HIT

Evaluation of hemoptysis:
- CXR
- Fiberoptic bronchoscopy
- CT scan of the chest

C. Treatment

1. Treat the underlying cause.
2. Suppress the cough if aggravating the hemoptysis.
3. Correct bleeding diathesis (although anticoagulation is the treatment for PE).
4. Monitor degree of respiratory compromise closely.

Diseases of the Gastrointestinal System

3

Kelley Chuang

Diseases of the Colon

Colorectal Cancer

A. General Characteristics

1. Third most common cancer in the world in men and second most common in women
2. Virtually, all colorectal tumors arise from adenomas. Majority are endoluminal adenocarcinomas arising from the mucosa. Rarely, carcinoid tumors, lymphomas, and Kaposi sarcoma may be present

Quick HIT

Colon cancer screening begins at age 45. If a first-degree relative has a history of colon cancer or advanced polyp, begin screening at age 40, or 10 years before age of onset of family member (whichever is earlier).

3. Screening—refer to Chapter 12, Ambulatory Medicine
   a. Stool-based screening tests
      - Fecal occult blood testing (FOBT) has poor sensitivity and specificity. Positive predictive value is only about 20%, but all patients with positive FOBT need a colonoscopy regardless
      - Fecal immunochemical tests (FIT) detect human hemoglobin and are more sensitive and specific for colorectal cancer (CRC) than FOBT. Screening is done yearly but requires colonoscopy if

positive. More convenient than colonoscopy, so FIT has improved adherence

b. Direct visualization tests

Colonoscopy: **most sensitive and specific test;** the diagnostic study of choice for patients with a positive FOBT or FIT. Both diagnostic and therapeutic (e.g., biopsy, polypectomy). Requires bowel preparation and sedation

- Flexible sigmoidoscopy: excellent sensitivity for distal colon where 50% to 60% of polyps and cancers occur (but may miss up to 45% of CRCs in the right side of colon). Requires enema preparation, less invasive than colonoscopy
- CT colonography: noninvasive imaging to visualize bowel mucosa by constructing 2-D and 3-D images of bowel mucosa. Variable sensitivity for polyps, poor sensitivity for flat or sessile polyps. Requires bowel preparation. If lesion found, still requires colonoscopy
- Colon capsule: minimally invasive study, limited for detecting larger polyps. Requires bowel preparation. If lesion found, still requires colonoscopy

c. Other tests (not for screening):

- Carcinoembryonic antigen (CEA)—not useful for screening; only useful in confirmed cases of CRC for establishing baseline, monitoring treatment efficacy, and recurrence surveillance. CEA does have prognostic significance: patients with preoperative CEA >5 ng/mL have a worse prognosis
- Barium enema is not recommended for screening

Quick HIT

Note that some CRCs may bleed intermittently or not at all.

4. Clinical TNM staging is done with CT scan of chest, abdomen, and pelvis and by physical examination (ascites, hepatomegaly, lymphadenopathy)
5. Pattern of spread

a. Direct extension—circumferentially and then through the bowel wall to later invade other abdominoperineal organs
b. Hematogenous
   - Portal circulation to liver—**liver is the most common site of distant spread**
   - Lumbar/vertebral veins to lungs
c. Lymphatic—regionally
d. Transperitoneal and intraluminal

Quick HIT

About 20% of patients have distant metastatic disease at presentation.

B. Risk Factors

1. Age—everyone over the age of 45 years is at increased risk
2. Adenomatous polyps
   a. These are premalignant lesions, but most do not develop into cancer.
   b. Villous adenomas have higher malignant potential than tubular adenomas.
   c. The larger the size, and the greater the number of polyps, the higher the risk of cancer.
3. Personal history of prior CRC or adenomatous polyps
4. Inflammatory bowel disease (IBD)
   a. Both ulcerative colitis (UC) and Crohn disease pose an increased risk for CRC, but UC poses a greater risk than Crohn disease
   b. Incidence of CRC rises with time since diagnosis of UC or Crohn disease and extent of colitis. Begin surveillance colonoscopy for CRC 8 years following the diagnosis of IBD
5. Family history of CRC
   a. Multiple first-degree relatives with CRC.
   b. Any first-degree relative diagnosed with CRC or adenoma under age 50
6. Dietary factors
   a. High-fat, low-fiber diets associated with a higher risk of CRC
7. Hereditary polyposis syndromes

a. **Familial adenomatous polyposis (FAP)**
   - Autosomal dominant disease caused by hereditary mutations in the adenomatous polyposis coli (APC) tumor suppressor gene
   - Characterized by hundreds of adenomatous polyps in the colon. The colon is always involved, and the duodenum is involved in 90% of cases. Polyps may also form in the stomach, jejunum, and ileum
   - In all FAP cases, the risk of CRC is 100% by the third or fourth decade of life.
   - Prophylactic colectomy is usually recommended

b. **Gardner syndrome**
   - Variant of FAP, autosomal dominant
   - Polyps plus osteomas, dental abnormalities, benign soft tissue tumors, desmoid tumors, sebaceous cysts
   - Risk of CRC is 100% by approximately age 40

c. **Turcot syndrome**
   - Variant of FAP, can be inherited as autosomal dominant or recessive
   - Polyps plus cerebellar medulloblastoma or glioblastoma multiforme

d. **Peutz–Jeghers**
   - Autosomal dominant
   - Single or multiple hamartomas that may be scattered through the entire GI tract: in small bowel (up to 90%), colon (60%), stomach (30%)
   - **Pigmented spots around lips, oral mucosa, face, genitalia, and palmar surfaces.**
   - Unlike adenomas, hamartomas have a very-low malignant potential
   - Increased risk of GI cancers (gastric, small bowel, colorectal, pancreas). Also increased risk of extraintestinal carcinomas (e.g., ovary, breast, cervix, testicle, lung). Most common non-GI cancer is breast cancer
   - Intussusception or GI bleeding may occur

e. **Familial juvenile polyposis coli**
   - Very rare autosomal dominant condition; presents in childhood.

- Only small risk of CRC
- Between 10 and hundreds of juvenile colon polyps

f. **Hereditary nonpolyposis CRC**—without adenomatous polyposis

- **Lynch syndrome I** (site-specific CRC)—early-onset CRC; absence of antecedent multiple polyposis
- **Lynch syndrome II** (cancer family syndrome)—all features of Lynch I plus increased number and early occurrence of other cancers (e.g., female genital tract, skin, stomach, pancreas, brain, breast, biliary tract)
- CRC screening begins much earlier (usually around ages 20 to 25)

C. Clinical Features

1. The presence of symptoms is typically a manifestation of advanced disease and worse prognosis. Symptoms include melena or hematochezia, abdominal pain, change in bowel habits, or unexplained iron-deficiency anemia
2. Signs and symptoms potentially common to all locations
   a. **Abdominal pain** is the most common presenting symptom. Can be caused by partial obstruction or peritoneal dissemination. Remember that **CRC is the most common cause of large bowel obstruction in adults.** Colonic perforation can lead to peritonitis and is the most life-threatening complication
   b. Weight loss
   c. Blood in stool
   d. Iron-deficiency anemia
   e. May be asymptomatic

Quick HIT

The sensitivity of individual symptoms for diagnosing CRC is poor.

3. Signs and symptoms based on specific location of tumor
   a. Right-sided tumors
   - Obstruction is unusual because of the **larger luminal diameter** allowing for large tumor growth to go undetected. The cecum has the largest luminal diameter of any part of the colon.

- Common findings: occult blood in stool, iron-deficiency anemia, weight loss, and **melena.**
- **Change in bowel habits is less common.**
- Triad of anemia, weakness, right lower quadrant (RLQ) mass may occasionally be present.

b. Left-sided tumors

- Smaller luminal diameter—signs of obstruction more common
- Change in bowel habits more common—alternating constipation/diarrhea; narrowing of stools ("pencil stools")
- Hematochezia more common
- Rectal tenesmus more common
- Rectal cancer (20% to 30% of all CRCs)
- Symptoms include hematochezia (most common), tenesmus, rectal mass, and feeling of incomplete evacuation of stool due to mass

Quick HIT

Right side: Melena is more common. Left side: Hematochezia is more common.

Quick HIT

Rectal cancer has a higher recurrence rate and a lower 5-year survival rate than colon cancer.

D. Treatment

1. Surgery is the only curative treatment of localized CRC. Surgical resection of tumor-containing bowel as well as resection of regional lymphatics
2. CEA level should be obtained before surgery (see below)
3. Utility of adjuvant therapy (chemotherapy or radiation therapy) depends on the stage of tumor and is beyond the scope of this book
4. Follow-up is important, and varies among physicians

   a. Annual CT scan of chest, abdomen, and pelvis for up to 5 years

   b. Colonoscopy at 1 year and then every 3 to 5 years

c. CEA levels are checked periodically (every 3 to 6 months)
   - A subsequent increase in CEA is a sensitive marker of recurrence
   - Often, second-look operations are based on high CEA levels postresection
   - Very high elevations of CEA suggest liver involvement

5. About 90% of recurrences occur within 3 years after surgery

Quick HIT

Radiation therapy is **not** routinely used in the treatment of colon cancer, although it is used in treating rectal cancer.

Colonic Polyps

A. Nonneoplastic Polyps—benign lesions with no malignant potential

1. Hyperplastic (metaplastic) polyps are the most common (90%) nonneoplastic polyps; generally remain small and asymptomatic.
2. No specific therapy required, but they can be difficult to distinguish from neoplastic polyps and so are commonly removed.
3. Juvenile polyps (typically in children younger than 10 years) are highly vascular and common, so they should be removed.
4. Inflammatory polyps (pseudopolyps) are associated with IBD.

Quick HIT

Polyps may be isolated or may occur as part of inherited polyposis syndromes, which have very high malignant potential.

B. Adenomatous Polyps—benign lesions, but have significant malignant potential; precursors of adenocarcinoma.

1. Can be one of three histologic types of adenoma
   a. Tubular (most common; up to 80% of cases)—smallest risk of malignancy

   b. Tubulovillous—intermediate risk of malignancy
   c. Villous—greatest risk of malignancy
2. Can determine malignant potential by the following:
   a. Size—the larger the polyp, the greater the malignant potential
   b. Histologic type
   c. Degree of dysplasia
   d. Shape—sessile (base and top of polyp have same diameter, more likely to be malignant), flat (difficult to detect), depressed (lower than surrounding mucosa, more likely to be malignant), or pedunculated (on a stalk)

Quick HIT

- Most polyps are found in the rectosigmoid region.
- Most patients are asymptomatic.
- In symptomatic patients, rectal bleeding is the most common symptom.

C. Treatment—complete polypectomy. If found to have high-risk features (dysplasia, numerous polyps, larger polyp size, or high-risk histology), surveillance colonoscopy at more frequent interval is recommended.

Diverticulosis

A. General Characteristics

1. Caused by **increased intraluminal pressure**—inner layer of colon bulges through the focal area of weakness in the colon wall (usually an area of blood vessel penetration)
2. Risk factors
   a. **Low-fiber, high-fat diets:** Constipation causes intraluminal pressures to increase.
   b. Physical inactivity
   c. Obesity
3. Prevalence increases with age

4. **The most common location is the sigmoid colon.** However, diverticula may occur anywhere in the colon

> **Quick HIT**
>
> Diverticulosis (pouches in the colon wall) should be distinguished from diverticulitis (inflammation or infection of diverticula). Diverticulitis is a complication of diverticulosis.

B. Clinical Features

1. Usually asymptomatic and discovered incidentally on imaging (e.g., CT abdomen/pelvis) or when a complication occurs (diverticular bleed or diverticulitis)
2. Vague left lower quadrant (LLQ) discomfort, bloating, constipation/diarrhea may be present
3. Only 10% to 20% become symptomatic (i.e., develop complications—see below)

C. Diagnosis

1. Barium enema or CT abdomen/pelvis (often incidentally found)
2. Abdominal x-rays are usually normal and are not diagnostic for diverticulosis

> **Quick HIT**
>
> - Complications of **diverticulosis** include painless rectal bleeding and diverticulitis.
> - Complications of **diverticulitis** include bowel obstruction, abscess, and fistulas.

D. Treatment

1. High-fiber diet to increase stool bulk and reduce constipation
2. Dietary fiber supplements (such as psyllium)

E. Complications

1. Painless rectal bleeding (up to 40% of patients)

a. Bleeding usually stops spontaneously. No further treatment is necessary in these patients.
b. Bleeding can be severe in about 5% of patients. Colonoscopy may be performed to locate and treat the site of bleeding (tagged RBC scan in certain cases if colonoscopy does not localize the site). If bleeding is persistent and/or recurrent, surgery (segmental colectomy) may be needed.

CLINICAL PEARL 3-1

Complications of Diverticulitis

- Abscess formation (can be drained either percutaneously under CT guidance or surgically)
- Colovesical fistula—accounts for 50% of fistulas secondary to diverticulitis; 50% close spontaneously
- Obstruction—due to chronic inflammation and thickening of bowel wall
- Free colonic perforation—uncommon but catastrophic (leads to peritonitis)

2. **Diverticulitis** (15% to 25% of patients)
   a. Occurs when feces become impacted in the diverticulum, leading to erosion and microperforation.
   b. Can be complicated (see also Clinical Pearl 3-1) or uncomplicated. Uncomplicated diverticulitis accounts for most cases and refers to diverticulitis without the complications listed in Clinical Pearl 3-1.
   c. Clinical features: fever, LLQ pain, leukocytosis.
      - Other possible features: alteration in BOWEL habits (constipation or diarrhea), vomiting, and sometimes a painful mass on rectal examination if inflammation is near the rectum.
   d. Diagnostic tests
      - **CT scan (abdomen and pelvis) with oral and IV contrast is the test of choice;** it may reveal a swollen, edematous bowel wall or an abscess.
      - Abdominal radiographs help in excluding other potential causes of LLQ pain, and can rule out ileus or obstruction (indicated by air–fluid levels, distention), and perforation (indicated by free air).

- **Avoid barium enema and colonoscopy during acute diverticulitis due to the risk of perforation.**

e. Treatment

- Uncomplicated diverticulitis: managed with antibiotics, bowel rest (NPO), IV fluids, and pain control. Mild episodes can be treated on outpatient basis with oral antibiotics if patient has reliable follow-up and has few or no comorbid conditions. If symptoms persist after 3 to 4 days, surgical resection of the involved segment may be necessary. Antibiotics are generally continued for 7 to 10 days. After successful treatment, about one-third has recurrence. Surgery recommended for recurrent episodes.
- Complicated diverticulitis: IV antibiotics, bowel rest (NPO), IV fluids. Surgery is often indicated for complications (perforation, large abscess, fistula). Antibiotics are usually continued for 10 to 14 days, but may be shorter if definitive source control is obtained (e.g., abscess drainage).

Quick HIT

- Diverticulitis recurs in about 30% of patients treated medically, usually within the first 5 years.

Quick HIT

- Diverticulosis—barium enema or CT scan are the tests of choice.
- Diverticulitis—CT scan is the test of choice (avoid barium enema and colonoscopy).

Quick HIT

A small percentage of patients with bleeding arteriovenous malformations have aortic stenosis (Heyde syndrome). However, no cause-and-effect relationship has been proven.

Quick HIT

- Acute mesenteric ischemia is sudden interruption of blood supply to the intestine. Chronic mesenteric ischemia is usually from chronic atherosclerotic disease of the splanchnic arteries.
- Patients with acute mesenteric ischemia often have pre-existing heart disease (e.g., congestive heart failure, CAD).

Angiodysplasia of the Colon (Arteriovenous Malformations, Vascular Ectasia)

- Tortuous, dilated veins in submucosa of the colon (usually proximal) wall.
- A common cause of **lower GI bleeding in patients over age 60**.
- Bleeding is usually low grade, but 15% of patients may have massive hemorrhage if veins rupture.
- Diagnosed by colonoscopy (preferred over angiography).
- In about 90% of patients, **bleeding stops spontaneously.**
- It can frequently be treated by colonoscopic hemostasis of the lesion. If bleeding persists, a right hemicolectomy should be considered.

Acute Mesenteric Ischemia

A. Introduction

1. Results from a compromised blood supply, usually to the superior mesenteric vessels.
2. There are four types (three are due to arterial disease, one due to venous disease):
   a. **Arterial embolism** (50% of cases): Almost all emboli are of a cardiac origin (e.g., atrial fibrillation, MI, valvular disease).
   b. **Arterial thrombosis** (25% of cases).
      - Most of these patients have atherosclerotic disease (e.g., coronary artery disease [CAD], PAD, stroke) at other sites.

- Acute occlusion occurs over pre-existing atherosclerotic disease. The acute event may be due to a decrease in cardiac output (e.g., resulting from MI, CHF) or plaque rupture.
- Collateral circulation has usually developed.

c. **Nonocclusive mesenteric ischemia** (20% of cases).
- Splanchnic vasoconstriction secondary to low cardiac output.
- Typically seen in critically ill elderly patients.

d. **Venous thrombosis** (<10% of cases). Many predisposing factors—infection, hypercoagulable states, oral contraceptives, portal HTN, malignancy, pancreatitis.

3. The overall mortality rate for all types of acute mesenteric ischemia is about 60% to 70%. If bowel infarction has occurred, the mortality rate can exceed 90%.

Quick HIT

Differences in Presentation of Types of Acute Mesenteric Ischemia:

- Embolic—symptoms are more sudden and painful than other causes
- Arterial thrombosis—symptoms are more gradual and less severe than embolic causes
- Nonocclusive ischemia—typically occurs in critically ill patients
- Venous thrombosis—symptoms may be present for several days or even weeks, with gradual worsening

B. Clinical Features

1. Classic presentation is acute onset of **severe abdominal pain out of proportion to physical examination findings.** Pain is due to ischemia and possibly infarction of intestines, analogous to MI in CAD.
   a. The abdominal examination may appear benign even when there is severe ischemia. This can lead to a delay in diagnosis.
   b. The acuteness and the severity of pain vary depending on the type of acute mesenteric ischemia (see Quick Hit).
2. Anorexia, vomiting.
3. GI bleeding.
4. Peritonitis, sepsis, and shock may be present in advanced disease.

Quick HIT

- Signs of intestinal infarction include hypotension, tachypnea, lactic acidosis, fever, and altered mental status (eventually leading to shock).
- Check the lactate level if acute mesenteric ischemia is suspected.

C. Diagnosis

1. High clinical suspicion in patients with known risk factors (CAD, Afib, recent MI, etc.).
2. CT angiography of abdomen/pelvis is the test of choice. Can also evaluate for other etiologies of abdominal pain.
3. Mesenteric angiography is the definitive test of choice and is done if CT angiography is equivocal.
4. "Thumbprinting" can be seen on barium enema due to thickened edematous mucosal folds.

D. Treatment

1. Supportive measures: IV fluids, broad-spectrum antibiotics, and pain management.
2. Avoid vasopressors, which may exacerbate ischemia.
3. Anticoagulation with unfractionated heparin.
4. Surgery (resection of nonviable bowel or embolectomy) may be needed if signs of peritonitis develop.
5. Catheter-directed interventions can be done if hemodynamically stable, no peritoneal signs, and low suspicion for advanced bowel ischemia. These include catheter-directed pharmacologic and mechanical thrombolysis, angioplasty, and stenting.
6. Direct intraarterial infusion of papaverine (vasodilator) into the superior mesenteric system during arteriography is an option for nonocclusive mesenteric ischemia.

Chronic Mesenteric Ischemia

- Caused by **atherosclerotic occlusive disease** of main mesenteric vessels (celiac artery, superior and inferior mesenteric arteries).

- Abdominal angina—dull pain, typically **postprandial** (when there is increased demand for splanchnic blood flow); analogous to anginal pain of CAD.
- Significant **weight loss** may occur due to abdominal angina.
- **CT abdomen with IV contrast is the initial test of choice.** Mesenteric arteriography confirms the diagnosis if CT is equivocal, and can be used for therapeutic intervention.
- Options for definitive treatment include surgical revascularization or mesenteric angioplasty and stenting. Revascularization leads to pain relief in 90% of cases.

Quick HIT

Patients with acute colonic pseudo-obstruction are usually ill and commonly have a history of recent surgery or medical illness.

Acute Colonic Pseudo-Obstruction (Ogilvie Syndrome)

- An unusual problem in which signs, symptoms, and radiographic evidence of large bowel obstruction are present, but **there is no mechanical obstruction.**
- Common causes include recent surgery or trauma, electrolyte serious medical illnesses (e.g., sepsis, malignancy, dementia, MI, metabolic derangements), and medications (e.g., opioids, psychotropic drugs, anticholinergics).
- The diagnosis cannot be confirmed until mechanical obstruction of the colon is excluded.
- Treatment consists of stopping any offending agent and supportive measures (IV fluids, electrolyte repletion, NG tube decompression, serial abdominal examinations).
- Neostigmine can be given if supportive measures are not effective. Decompression with gentle enemas or nasogastric suction may be helpful. Colonoscopic decompression is usually successful if the above measures fail.
- Surgical decompression with cecostomy or colostomy is a last resort.

Quick HIT

Whenever there is colonic distention and the colon diameter exceeds 10 cm, bowel is at risk of impending rupture leading to peritonitis and even death; **decompress immediately.**

Colonic Volvulus

A. General Characteristics

1. Defined as twisting of a loop of intestine about its mesenteric attachment site.
2. May result in obstruction or vascular compromise with the potential for necrosis and/or perforation if untreated.
3. Worldwide, the **most common site is the sigmoid colon** (75% of all cases).
4. Cecal volvulus accounts for 25% of all cases.
5. Risk factors
   a. Chronic illness, age, institutionalization, and CNS disease increase risk of sigmoid volvulus.
   b. Cecal volvulus is due to congenital lack of fixation of the right colon and tends to occur in younger patients.
   c. Chronic constipation, laxative abuse, antimotility drugs.
   d. Prior abdominal surgery.

B. Clinical Features

1. Acute to subacute onset of colicky abdominal pain
2. Obstipation, abdominal distention and tenderness
3. Anorexia, nausea, vomiting

C. Diagnosis

1. Plain abdominal films—identifies sigmoid volvulus in 60% of cases.
   a. Sigmoid volvulus—classic finding is *Omega loop sign* (or bent inner-tube shape), indicates a dilated sigmoid colon.
   b. Cecal volvulus (distention of cecum and small bowel)—classic finding is *coffee bean sign,* indicates a large air–fluid level in RLQ.

2. CT of abdomen—typical pattern is *"whirl sign"* caused by dilated colon twisting around mesenteric vessels (see Figure 3-1). May also show absence of rectal gas. Can identify complications (pneumatosis intestinalis, portal venous gas).
3. Sigmoidoscopy—preferred diagnostic and therapeutic test for **sigmoid volvulus** (not for cecal volvulus); leads to successful treatment (untwisting and decompression) in many cases.
4. Barium enema—reveals the narrowing of the colon at the point where it is twisted (*"bird's beak"*).

Quick HIT

Do not perform a barium enema if perforation is suspected!

D. Treatment

1. Sigmoid volvulus: Nonoperative reduction (decompression via sigmoidoscopy) is successful in >75% of cases. The recurrence rate is high, so elective sigmoid colon resection is recommended.
2. Cecal volvulus: Emergent surgery is indicated.

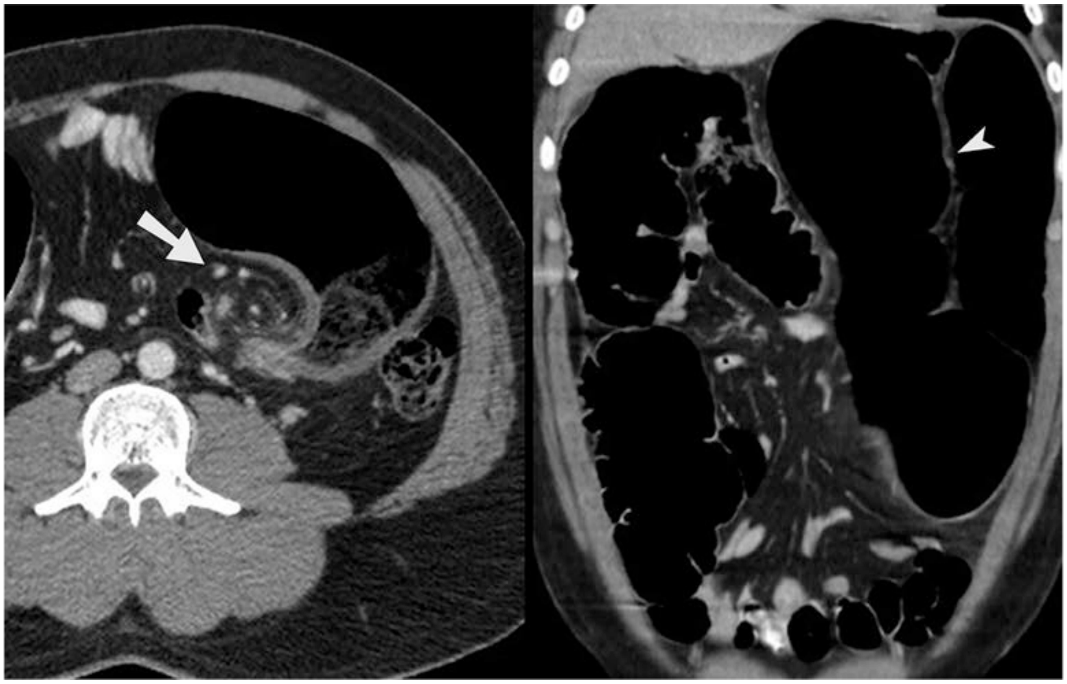


FIGURE 3-1 **Axial contrast-enhanced CT of the abdomen demonstrating sigmoid volvulus with the whirl sign (*arrow*) at site of torsion. On right, coronal CT showing dilated sigmoid colonic loop in the left upper quadrant, with two walls opposed together (*arrowhead*).**
(Reprinted with permission from Singh AK. *Gastrointestinal Imaging: The Essentials*. Wolters Kluwer; 2016. Figure 5A.22.)

Diseases of the Liver

Acute Liver Failure

A. General Characteristics

1. Acute liver failure refers to an acute, severe liver injury with concurrent encephalopathy and impaired synthetic liver function.
2. In order to diagnose, patients must not have underlying liver disease or cirrhosis prior to insult.
3. Typically, time course of illness is less than 26 weeks.

B. Causes

1. A large number of insults can cause acute liver failure. Most notably are as follows:
   a. **Acetaminophen**
   b. Drug reactions
   c. Viral hepatitis
   d. Autoimmune hepatitis
   e. Wilson disease
   f. Ischemic hepatopathy
   g. Budd–Chiari disease
   h. Acute fatty liver of pregnancy/HELLP syndrome
   i. Malignancy
   j. Sepsis
   k. Toxins

C. Diagnosis

1. Diagnosis requires three components: encephalopathy, INR ≥ 1.5 (impaired synthetic liver function) and elevated liver enzymes.
2. Patients may also present with jaundice, hepatomegaly, abdominal tenderness, and thrombocytopenia.
3. Etiology of disease can be determined through a thorough history (especially medications and supplements, toxins, risk factors for viral hepatitis, family history, and alcohol use history), physical examination, laboratory tests, and imaging studies (CT abdomen/pelvis, MRI, abdominal US). A liver biopsy may be necessary.

Quick HIT

Signs of Acute Liver Failure (any of the following may be present):

- Coagulopathy
- Jaundice
- Hypoglycemia (liver stores glycogen)
- Electrolyte abnormalities (hypophosphatemia, hypomagnesemia, hypokalemia)
- Acid–base disorders (either acidosis or alkalosis)
- Hepatic encephalopathy
- Infection
- Elevated transaminases and bilirubin
- Any complication associated with cirrhosis

D. Management

1. Patients should be watched closely (preferably at a liver transplantation center) as they can quickly decompensate. Eligibility for liver transplant should be considered early, although 40% of patients will recover with supportive care (nutritional support and treating complications). Probability of spontaneous recovery depends on age, degree of encephalopathy, and cause of liver failure.
2. Treat underlying cause if applicable.
3. Encephalopathy—monitor with neurologic checks every 2 hours. Consider lactulose therapy, although not shown to improve overall outcomes.
4. Cerebral edema may cause elevated intracranial pressure (ICP) and brainstem herniation (a major cause of morbidity and mortality). Consider monitoring ICP in patients with advancing encephalopathy. Treat elevated ICP with mannitol.
5. Liver transplantation. Several models exist to predict outcome and prioritize for transplantation, including MELD score and King's College Criteria. 1-year survival posttransplant is 80%.

A 52-year-old woman presents with confusion that has worsened over the past week. Her partner reports that she has also noticed yellowing of the skin. Further history reveals that the patient has been taking over-the-counter medications for chronic pain. The patient drinks three glasses of wine per night and reports no illicit drug use. Physical examination is significant for tenderness to palpation in the right upper quadrant and hepatomegaly. Laboratory results reveal the following.

Total bilirubin	7.1 mg/dL
Direct bilirubin	4.2 mg/dL
Aspartate aminotransferase	5,424 U/L
Alanine aminotransferase	6,934 U/L
Alkaline phosphatase	120 U/L
Prothrombin time	31 s
Partial thromboplastin time	44 s
INR	1.9

Which of the following is the underlying diagnosis?

A. Drug-induced acute liver failure
B. Acute alcoholic hepatitis
C. Nonalcoholic fatty liver disease
D. Chronic viral hepatitis

- **The answer is A: Drug-induced acute liver failure.** This patient is presenting with signs and symptoms consistent with a diagnosis of acute liver failure. Acute liver failure is distinguished by severely elevated transaminases, defective hepatic synthesis (coagulation abnormalities), and hepatic encephalopathy. Given this patient’s history of over-the-counter pain medications (likely acetaminophen), the diagnosis is likely drug-induced acute liver failure. Acetaminophen levels should be measured and the patient should

begin treatment with *N*-acetylcysteine. **(B)** Acute alcoholic hepatitis alone usually only causes a mild to moderate elevation of AST and ALT levels. In addition, the AST:ALT ratio is usually greater than 2:1. **(C)** Nonalcoholic fatty liver disease is usually asymptomatic and presents with only mild elevations of AST and ALT levels. **(D)** Similar to nonalcoholic liver disease, chronic viral hepatitis is associated with mild elevations of AST and ALT levels and will not present with abnormal coagulation studies or hepatic encephalopathy.

TABLE 3-1 Child–Pugh Classification to Assess Severity of Liver Disease

	POINTS		
	1	**2**	**3**
Ascites	None	Slight	Moderate
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Encephalopathy	None	Mild–moderate	Severe
INR ratio	<1.7	1.7–2.3	>2.3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8

Class A—5–6 points total (least severe liver disease), 85% 2-year survival
Class B—7–9 points total (moderate–severe liver disease), 60% 2-year survival
Class C—10–15 points total (severe liver disease), 35% 2-year survival

Cirrhosis

A. General Characteristics

1. Cirrhosis is a chronic liver disease characterized by fibrosis, disruption of the liver architecture, and widespread nodules in the liver. The fibrous tissue replaces damaged or dead hepatocytes.
2. Cirrhosis is generally irreversible when advanced. In early stages, specific treatment of the cause of cirrhosis may improve or reverse the

condition. The point at which the disease becomes irreversible is not clear.

3. The distortion of liver anatomy causes two major events.
   a. Decreased blood flow through the liver with subsequent hypertension in portal circulation **(portal hypertension)**—this has widespread manifestations, including ascites, peripheral edema, splenomegaly, and varicosity of veins "back stream" in the circulation (e.g., gastric/esophageal varices, hemorrhoids).
   b. **Hepatocellular failure** that leads to impairment of biochemical functions, such as decreased albumin synthesis and decreased clotting factor synthesis.
4. Assessment of hepatic functional reserve.
   a. **Child–Pugh classification** (see Table 3-1) estimates hepatic reserve in liver failure. It is used to measure disease severity and is a predictor of morbidity and mortality.
   b. Child's class C indicates most severe disease, and Child's class A indicates milder disease.
   c. **Model for End-Stage Liver Disease (MELD) score** is a severity scale to predict 3-month survival. Scoring is also used to prioritize patients awaiting liver transplant. Calculation depends on patient's serum bilirubin, serum creatinine, and INR. An increased MELD score in cirrhotic patients is associated with an increased 3-month mortality risk.
   d. The MELD-Na score adds serum sodium into the calculation, as many patients with cirrhosis have hyponatremia (degree of hyponatremia correlates with severity of cirrhosis). May provide better prognostication for patients awaiting liver transplant.

B. Causes

1. **Alcoholic liver disease**
   a. Refers to a range of conditions from fatty liver (alcohol-associated steatosis, reversible, due to acute ingestion) to cirrhosis (irreversible)
   b. Approximately 8% to 20% of patients with alcohol-associated steatosis will progress to cirrhosis
2. **Chronic hepatitis B and C infections**
3. Nonalcoholic fatty liver disease (NAFLD)

4. Drugs (e.g., acetaminophen toxicity, methotrexate)
5. Autoimmune hepatitis
6. Primary biliary cholangitis (PBC), secondary biliary cirrhosis
7. Inherited metabolic diseases (e.g., hemochromatosis, Wilson disease)
8. Hepatic congestion secondary to right-sided heart failure, constrictive pericarditis
9. α1-Antitrypsin (AAT) deficiency
10. Hepatic veno-occlusive disease—can occur after bone marrow transplantation
11. Granulomatous liver disease

C. Clinical Features

1. Some patients have no overt clinical findings, especially early in the disease.
2. Nonspecific symptoms of anorexia, weight loss, weakness, and fatigue.
3. Patients may have signs or symptoms suggestive of one or more of the complications of cirrhosis (see below).

Quick HIT

Classic signs of chronic liver disease:
- Jaundice
- Ascites
- Varices
- Gynecomastia, testicular atrophy
- Palmar erythema, spider angiomas on skin
- Asterixis
- Hemorrhoids
- Splenomegaly
- Caput medusa

D. Complications

1. Portal HTN
   a. Classic signs of cirrhosis are most apparent when portal HTN occurs. **Bleeding** (hematemesis, melena, hematochezia) secondary to esophagogastric varices is the most life-threatening complication of portal HTN.

b. Diagnose based on classic physical features of cirrhosis. Labs may show thrombocytopenia, coagulopathy, and hypoalbuminemia. Ultrasound can identify nodular liver and confirm portal HTN.

c. Treat the specific complication. **Transjugular intrahepatic portosystemic shunt (TIPS)** can be used to lower portal pressure especially when managing esophageal varices or refractory ascites, but has significant risks (hepatic encephalopathy [HE], worsening heart failure, etc.).

2. Varices

a. Esophageal/gastric

- Variceal hemorrhage has a high mortality rate. Patients with cirrhosis should be evaluated with endoscopy for the presence of varices and risk of hemorrhage. **If varices are present, prophylactic measures are indicated (such as endoscopic banding or ligation, and nonselective β-blockers).**
- Clinical features include massive hematemesis, melena, and exacerbation of HE.
- Esophageal varices account for 85% of varices, and gastric varices for 15%.
- Initial treatment is hemodynamic stabilization (give fluids to maintain BP) and supportive blood product transfusion. See Clinical Pearl 3-2 for methods aimed at stopping bleeding.
- IV antibiotics are given for 7 days for prophylaxis of spontaneous bacterial peritonitis (SBP).
- IV octreotide to induce splanchnic vasoconstriction.
- Perform **urgent upper GI endoscopy** (once patient is stabilized) for diagnosis and to treat the hemorrhage either with variceal ligation or sclerotherapy.
- Give nonselective β-blockers (propranolol, timolol, nadolol) as long-term therapy to prevent rebleeding for selected patients.

b. Rectal hemorrhoids

c. *Caput medusae* (distention of abdominal wall veins)

CLINICAL PEARL 3-2

Treatment of Bleeding Esophageal Varices

- Variceal ligation/banding
- Initial endoscopic treatment of choice.
- Effective control of active bleeding.
- Lower rate of rebleeding than sclerotherapy.
- Endoscopic sclerotherapy
- Sclerosing substance is injected into varices during endoscopy.
- This controls acute bleeding in 80% to 90% of cases.
- Up to 50% of patients may have rebleeding.
- IV vasopressin
- This is an alternative to octreotide, but is rarely used due to the risk of complications.
- Vasoconstriction of mesenteric vessels reduces portal pressure.
- IV octreotide infusion
- Has replaced vasopressin as first-line therapy; causes splanchnic vasoconstriction and reduces portal pressure.
- Fewer side effects than vasopressin.
- Other options include esophageal balloon tamponade (Sengstaken–Blakemore tube is a temporary measure), repeat sclerotherapy, TIPS, surgical shunts, and liver transplantation.

CLINICAL PEARL 3-3

Differential Diagnosis of Ascites

- Cirrhosis, portal HTN
- CHF
- Chronic renal disease
- Massive fluid overload
- Tuberculous peritonitis
- Malignancy
- Hypoalbuminemia
- Peripheral vasodilation secondary to endotoxin-induced release of nitrous oxide, which leads to increased renin secretion (and thus secondary hyperaldosteronism)
- Impaired liver inactivation of aldosterone

Quick HIT

Once a patient develops complications of cirrhosis, they have "decompensated" disease, with high morbidity and mortality.

3. Ascites (see also Clinical Pearl 3-3)
   a. Accumulation of fluid in the peritoneal cavity due to **portal HTN** (increased hydrostatic pressure) and **hypoalbuminemia** (reduced oncotic pressure). Ascites is the most common complication of cirrhosis. Patients without portal hypertension do not develop ascites.
   b. Clinical features: abdominal distention, shifting dullness, and fluid wave.
   c. Abdominal ultrasound can detect as little as 30 mL of fluid.
   d. Diagnostic **paracentesis** determines whether ascites is due to portal HTN or another process.
      - Indications include new-onset ascites, worsening ascites, and suspected SBP (see below).
      - Initial ascites studies should include cell count and differential, albumin, total protein, Gram stain and culture to rule out infection (e.g., SBP).
      - Measure the **serum ascites albumin gradient (SAAG).** If it is >1.1 g/dL, portal HTN is very likely. If <1.1 g/dL, portal HTN is unlikely, and other causes must be considered.
   e. Treatment
      - Low-sodium diet and diuretics: spironolactone (used to reduce accumulation of fluid) and furosemide (used to preserve potassium balance).
      - Perform therapeutic paracentesis if tense ascites, shortness of breath, or early satiety is present.
      - TIPS to reduce portal HTN if diuretic-resistant ascites or requiring frequent therapeutic paracentesis (risk of worsening HE and other complications).

Quick HIT

Treatment of bleeding esophageal varices involves pharmacologic treatment with IV octreotide in addition to endoscopic treatment (sclerotherapy or variceal ligation). Don't forget SBP prophylaxis with antibiotics (ceftriaxone or ciprofloxacin).

Quick HIT

Ascites can be managed by salt restriction and diuretics in most cases.

Quick HIT

Complications of Chronic Liver Failure (note the mnemonic AC, 8H)

- Ascites
- Coagulopathy
- Hypoalbuminemia
- Portal hypertension
- Hepatic encephalopathy
- Hepatorenal syndrome
- Hypoglycemia
- Hyperbilirubinemia/jaundice
- Hyperestrinism
- HCC

4. HE
   a. Toxic metabolites (there are many, but **ammonia** is believed to be most important) that are normally detoxified or removed by the liver accumulate and reach the brain
   b. Occurs in 30% to 45% of all cases of cirrhosis, with varying severity
   c. Precipitants include infection, GI bleeding, metabolic derangements (alkalosis, hypokalemia, hypoglycemia), renal failure, hypovolemia, hypoxia, medications (sedatives), and constipation
   d. Clinical features
      - Range from subtle findings to overt symptoms
      - Decreased mental function, confusion, impaired attention, disturbance in sleep pattern, even stupor or coma

- *Asterixis* ("flapping tremor")—have the patient extend the arms and dorsiflex the hands. (However, this is not a specific sign.)
- Rigidity, bradykinesia, hyperreflexia
- Other signs of advanced liver disease (jaundice, ascites, palmar erythema, spider telangiectasias, *fetor hepaticus* or musty odor of breath)

e. Treatment

- Lactulose prevents absorption of ammonia. Metabolism of lactulose by bacteria in the colon favors formation of NH_4^+, which is poorly absorbed from GI tract, thereby promoting excretion of ammonia.
- Rifaximin (antibiotic): kills bowel flora; so decreases ammonia production by intestinal bacteria. Historically, neomycin was used, but rifaximin has less side effects with same efficacy.
- Diet—protein restriction is associated with increased mortality. Focus on optimizing nutrition with small frequent meals (patients with cirrhosis are often malnourished; fasting can increase ammonia production).

Quick HIT

Ammonia levels are not reliable to diagnose or rule out hepatic encephalopathy (level does not correlate with degree of HE). Diagnosis of HE is made based on signs and symptoms.

5. Hepatorenal syndrome—indicates end-stage liver disease
   a. Progressive renal failure in advanced liver disease.
   b. Portal hypertension leads to splanchnic vasodilation, which overall leads to upregulation of renin–angiotensin–aldosterone system. This leads to renal vasoconstriction and decrease in renal perfusion (see Figure 3-2).
   c. Often precipitated by infection or GI bleeding.
   d. This is a diagnosis of exclusion—kidneys have normal morphology, and no specific causes of renal dysfunction are evident. To diagnose, must confirm that renal function does not improve with volume expansion (stop diuretics and give albumin).

e. Clinical features: AKI, azotemia, no other causes of AKI (rule out shock, nephrotoxins, obstruction, hypovolemia, etc.)

f. Treatment:

- Medical therapy: goal is to improve renal perfusion. Octreotide (splanchnic vasoconstriction), midodrine or norepinephrine (systemic vasoconstriction), and albumin (volume expansion)
- Liver transplantation is the only definitive treatment. In general, the prognosis is very poor, and the condition is usually fatal without liver transplantation

Quick HIT

Monitoring Patients with Cirrhosis

- Order periodic laboratory values every 6 months (CBC, basic metabolic panel, hepatic panel, and coagulation tests) to track Child–Pugh and MELD scores
- Order right upper quadrant ultrasound +/– serum AFP every 6 months to screen for HCC
- Refer for endoscopy to determine the presence of esophageal varices

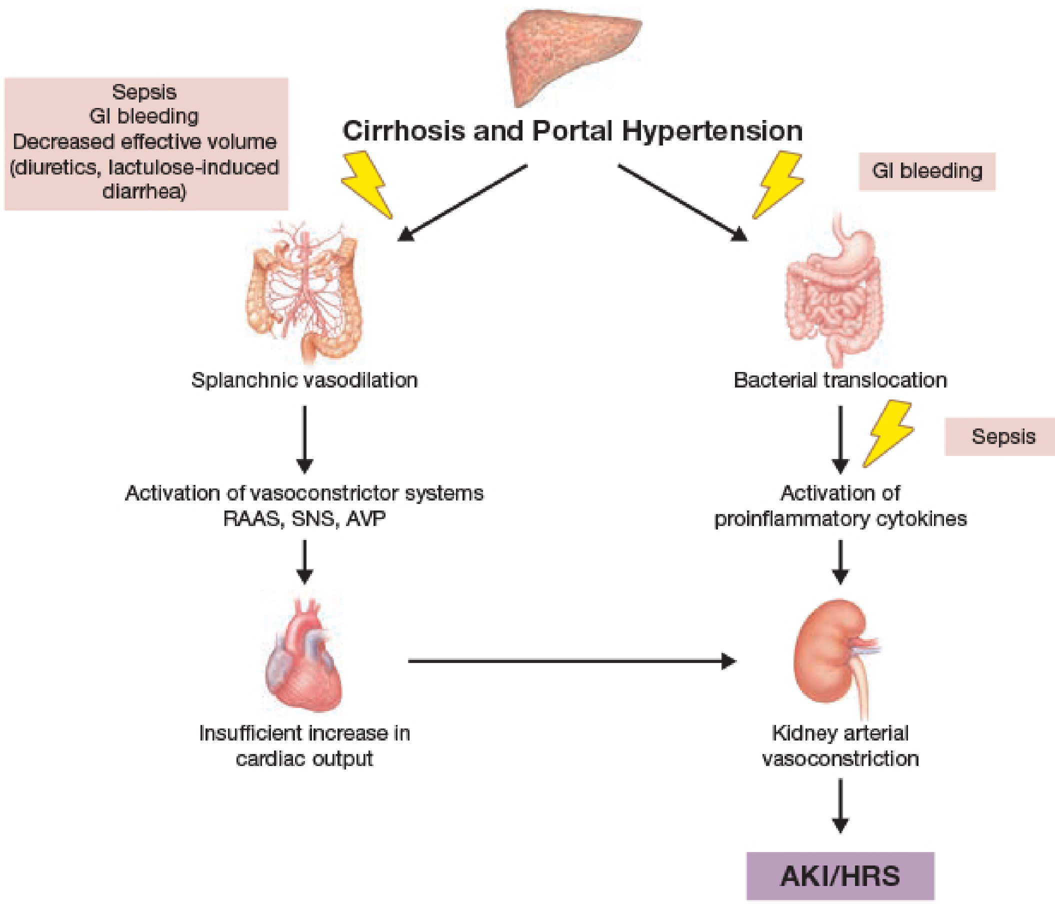


FIGURE 3-2 Mechanisms contributing to acute kidney injury (AKI) and hepatorenal syndrome (HRS) in decompensated cirrhosis.
(Reprinted with permission from Koyner JL, Topf JM, Lerma EV. *Handbook of Critical Care Nephrology*. Wolters Kluwer; 2021. Figure 42.1.)

6. SBP—Infected ascitic fluid; occurs in up to 30% of patients hospitalized with cirrhosis and ascites. Mechanism not fully understood but thought to be due to translocation of gut bacteria and endotoxins into ascites
   a. Usually occurs in patients with ascites caused by end-stage liver disease; associated with high mortality rate (20% to 40%)
   b. Has a high recurrence rate (up to 70% in first year)
   c. Etiologic agents. Mostly gut flora
      - *Escherichia coli* (most common)
      - *Klebsiella pneumoniae*
      - *Streptococcus species*

d. Clinical features: fever, abdominal pain and tenderness, altered mental status. SBP may lead to sepsis. Patients with cirrhosis may not mount a fever (may be baseline hypothermic) and may be asymptomatic, so have low threshold for diagnostic paracentesis

e. **Diagnosis is established by paracentesis and examination of ascitic fluid for WBCs (especially PMNs)**, Gram stain with culture, and sensitivities
- PMN $\geq$250 cells/mm^3
- Positive ascites culture; culture-negative SBP is common as well

f. Treatment
- Broad-spectrum antibiotic therapy: usually third-generation cephalosporin (ceftriaxone) or carbapenem for severe disease. Switch to narrow-spectrum antibiotic once organism is identified
- Give albumin to prevent renal failure
- Clinical improvement should be seen in 24 to 48 hours. Repeat paracentesis to document resolution of infection is usually not needed, unless patient does not respond to empiric treatment
- Patients should be offered long-term SBP prophylaxis after one episode (usually norfloxacin or ciprofloxacin)

Quick HIT

SBP: Look for fever, abdominal pain, or change in mental status in a patient with known ascites.

Quick HIT

If SBP is not treated early, mortality is high. Patients may not have overt symptoms. Therefore, index of suspicion should be high and diagnostic paracentesis should be done early.

7. Hyperestrinism—due to reduced hepatic catabolism of estrogens

a. *Spider angiomas*—dilated cutaneous arterioles with central red spot and reddish extensions that radiate outward like a spider's web

b. Palmar erythema

c. Gynecomastia

d. Testicular atrophy

8. Coagulopathy
   a. Patients can be at risk for both bleeding and clotting at the same time. Decreased synthesis of clotting factors, thrombocytopenia, and platelet dysfunction can increase bleeding risk. Decreased synthesis of protein C, S, and antithrombin can increase clotting risk. Fibrinolysis (dissolution of clot) is also altered.
   b. Prolonged prothrombin time (PT); PTT may be prolonged with severe disease. However, PT, PTT, and INR alone are not reliable indicators of bleeding or clotting risk in cirrhosis.
   c. Fibrinogen level may be low.
   d. Treatment with vitamin K, fresh frozen plasma (clotting factors), platelets, and cryoprecipitate (fibrinogen) should be reserved for bleeding or prior to invasive procedures. Do not routinely transfuse fresh frozen plasma to normalize coagulation tests.
9. Hepatocellular carcinoma (HCC)—all patients with cirrhosis (and chronic HBV without cirrhosis) are at risk. All patients with cirrhosis should be screened for HCC, most commonly with serum AFP measurement and liver ultrasound every 6 months.
   a. Diagnosis can be made by imaging when HCC is suspected: CT abdomen with IV contrast (triple phase CT) or MRI abdomen with contrast. Liver biopsy is often not necessary except for equivocal cases, and has risks.
   b. Treatment options include surgical resection, radiofrequency ablation, embolization, and liver transplantation.

E. Treatment

1. Treat underlying cause—for example, abstinence from alcohol, antiviral treatments for hepatitis B and C.
2. Avoid agents that may cause injury to liver, such as acetaminophen and alcohol.
3. Once cirrhosis develops, aim treatment at prevention and management of any complications that arise, as described above. The most serious complications are variceal bleeding, ascites, HE, and HCC. Advanced care planning is especially important for patients with cirrhosis.
4. Refer for liver transplantation for decompensated cirrhosis. Candidacy for and decision to proceed to liver transplantation depends on quality

of life, severity of disease, and absence of contraindications, among many other factors.

Wilson Disease

A. General Characteristics

1. An autosomal recessive disease of **copper metabolism.**
2. Mutations in the ATP7B gene lead to impairment of copper excretion into bile, and incorporation of copper into ceruloplasmin, a copper-binding protein that is necessary for copper excretion.
3. Therefore, copper accumulates in liver cells. As hepatocytes die, copper leaks into plasma and accumulates in various organs, including kidney, cornea, and brain.
4. The disease is most often apparent during childhood/adolescence (after age 5), and the majority of cases present between ages 5 and 35.

B. Clinical Features

1. Clinical features are due to copper deposition in various organs.
2. Liver disease (most common initial manifestation): Manifestations vary and may include acute hepatitis, cirrhosis, and fulminant hepatic failure.
3. *Kayser–Fleischer rings* (yellowish rings in cornea) are caused by copper deposition in cornea; they do not interfere with vision (Figure 3-3).
4. CNS findings are due to copper deposition in the CNS.
   a. Extrapyramidal signs—parkinsonian symptoms (tremor, rigidity, bradykinesia), chorea, dysarthria, incoordination due to copper deposition in basal ganglia.
   b. Psychiatric disturbances—depression, labile mood, impulsiveness, personality changes, psychosis.
5. Other organ involvement is less common. Renal (aminoaciduria, nephrolithiasis), cardiac (cardiomyopathy), among others.

Quick HIT

Alkaline phosphatase is normal or low in Wilson disease as copper interferes with its synthesis.

C. Diagnosis

1. Diagnosis is made by determining the following (patients may have many or only a few of these findings):
   a. Hepatic disease—elevated aminotransferases; impaired synthesis of coagulation factors and albumin
   b. Neuropsychiatric symptoms suggestive of Wilson disease
   c. Decreased serum ceruloplasmin levels (seen in 90% of patients), although ranges within normal do not exclude the diagnosis
   d. Elevated urinary copper excretion (by 24-hour urine copper)
   e. Liver biopsy—significantly elevated copper concentration
   f. If diagnosed, first-degree relatives must be screened as well

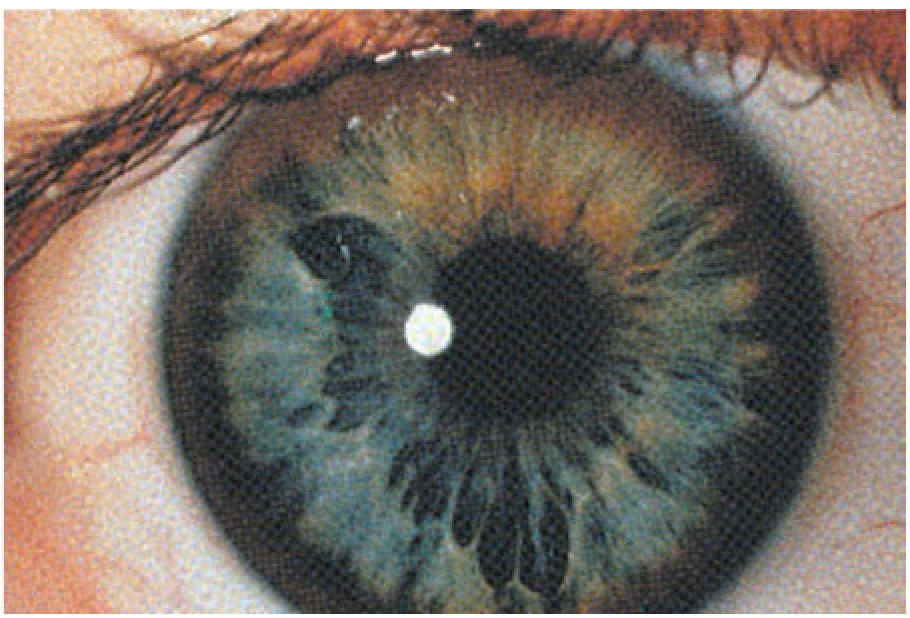


FIGURE 3-3 **Kayser–Fleischer ring.**
(Reprinted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000. Figure 105.4.)

D. Treatment

1. Chelating agents—for example, D-penicillamine, which removes and detoxifies the excess copper deposits
2. Zinc
   a. Prevents uptake of dietary copper
   b. Given alone (to presymptomatic patients) or in conjunction with chelating agents (to symptomatic patients)
3. Liver transplantation (if unresponsive to therapy or fulminant liver failure)
4. Monitor patient's copper levels, urinary copper excretion, ceruloplasmin, and liver function; physical examination for signs of liver or neurologic disease; psychological health

Quick HIT

Secondary hemochromatosis (iron overload) can occur with multiple transfusions or in chronic hemolytic anemias.

A 28-year-old man presents with fatigue and confusion. His girlfriend states that he has been “impulsive” and “not himself,” and has been forgetting the names of his close friends. Physical examination reveals mild tenderness to palpation in the RUQ, and a resting tremor in his upper extremities. Labs reveal elevation in transaminases.

Which of the following laboratory findings do you expect with this condition?

A. Elevated ferritin
B. Decreased serum ceruloplasmin
C. Decreased urinary copper
D. Elevated serum copper

- **The answer is B: Decreased serum ceruloplasmin.** The patient in this question is presenting with neuropsychiatric symptoms and transaminase elevation consistent with a diagnosis of Wilson disease. Wilson disease is an autosomal recessive disorder in which copper accumulates in tissues due to mutations in the Wilson disease protein (ATP7B) gene; this causes a defect in incorporation of copper in hepatic lysosomes. The main sites of copper accumulation are the liver and the brain. The faulty incorporation of copper in the liver leads to defective synthesis of ceruloplasmin, a protein carrier of copper. The resulting high unbound copper in the serum causes deposits in the cornea, liver, and several neurologic structures (basal ganglia, brainstem, cerebral cortex, etc.). **(C, D)** The diagnosis of Wilson disease is based on laboratory findings: high urinary copper, low serum ceruloplasmin, low serum copper (the low ceruloplasmin causes the bound portion of copper to be low), and high hepatic copper content on liver biopsy. **(A)** Elevated ferritin is associated with hereditary hemochromatosis, an autosomal recessive disorder of iron overload (not copper).

Hemochromatosis

A. General Characteristics

1. An autosomal recessive disease of iron absorption
2. Excessive iron absorption in the intestine leads to increased accumulation of iron (as ferritin and hemosiderin) in various organs. Over many years, fibrosis in involved organs occurs secondary to hydroxyl free radicals that are generated by the excess iron
3. Affected organs
   a. Liver (primary organ)
   b. Pancreas
   c. Heart
   d. Joints
   e. Skin
   f. Thyroid, gonads, hypothalamus
4. This is an inherited disease, so screen the patient's first-degree relatives. Early diagnosis and treatment before development of complications (primarily cirrhosis, but also heart disease and diabetes) improve survival

Quick HIT

Hemochromatosis: Early in the disease course, mild elevation of ALT and AST levels may be the only abnormalities that are noted because the patient is usually asymptomatic. Obtain iron studies. If the transferrin saturation and ferritin are elevated, order an MRI, which can diagnose elevated iron stores without need for liver biopsy.

B. Clinical Features

1. Most patients are asymptomatic initially.
2. Findings may include signs of liver disease, fatigue, arthritis, impotence/amenorrhea, abdominal pain, and cardiac arrhythmias.

C. Complications

1. Cirrhosis
   a. Cirrhosis increases the risk of HCC by 200-fold

b. The presence of liver disease is a primary factor in determining the prognosis

2. Cardiomyopathy—CHF, arrhythmias
3. Diabetes mellitus—due to iron deposition in the pancreas
4. Arthritis—most common sites are the second and third metacarpophalangeal joints, hips, and knees
5. Hypogonadism—impotence, amenorrhea, loss of libido
6. Hypothyroidism
7. Hyperpigmentation of skin (“bronze diabetes”)

D. Diagnosis

1. Markedly elevated serum iron and serum ferritin
2. Elevated iron saturation (transferrin saturation)
3. Decreased total iron-binding capacity (TIBC)
4. Genetic testing for etiologic mutations (gold standard for diagnosis)
5. Estimation of iron stores with MRI

E. Treatment

1. **Perform repeated therapeutic phlebotomies**—this is the treatment of choice and improves survival dramatically if initiated early in the course of the disease.
2. Treat any complications (e.g., CHF, diabetes, hypothyroidism, arthritis).
3. Consider liver transplantation in advanced cases.

Hepatocellular Adenoma

- Benign liver tumor, most often seen in young women (15 to 40 years of age) or individuals with estrogen use. Use of estrogens (e.g., oral contraceptives), female sex, and anabolic steroid use are the main risk factors.
- Patient may be asymptomatic; hepatocellular adenoma may be discovered incidentally on abdominal imaging studies. RUQ pain or fullness may be present.
- Malignant potential is very low (<1%). However, the adenoma may rupture, leading to hemoperitoneum and hemorrhage.
- Diagnosis made by CT scan, ultrasound, or MRI.

- Treatment: Discontinue estrogen-containing medications; surgically resect tumors >5 cm that do not regress after stopping estrogen (otherwise there is a risk of rupture).

Hepatic Hemangiomas

- Vascular tumors that are usually small and asymptomatic. They are the **most common type of benign liver tumor**.
- As the size of the tumor increases (e.g., due to pregnancy or use of estrogen therapy), the symptoms increase and include RUQ pain or mass.
- Complications (uncommon unless tumor is very large) include rupture with hemorrhage, obstructive jaundice, coagulopathy, CHF secondary to a large AV shunt, and gastric outlet obstruction.
- Diagnose with ultrasound, CT scan with IV contrast, or MRI. Biopsy contraindicated because of risk of rupture and hemorrhage.
- Most cases do not require treatment. Consider resection if the patient is symptomatic or if there is a high risk of rupture (as with large tumors).

Focal Nodular Hyperplasia

- This benign liver tumor without malignant potential occurs mostly in women. **There is no association with estrogen therapy (e.g., oral contraceptives).**
- It is usually asymptomatic. Hepatomegaly may be present. Treatment not necessary in most cases.

Hepatocellular Carcinoma (Malignant Hepatoma)

A. General Characteristics

1. HCC accounts for more than 80% of primary liver cancers and is a top cause of cancer-related deaths in the world. Highest-risk area is Asia (HBV endemic areas).
2. There are two pathologic types
   a. Nonfibrolamellar (most common)
      - Usually associated with hepatitis B or C and cirrhosis

- Usually unresectable with very short survival time (months)

b. Fibrolamellar (rare)
- Usually **not** associated with hepatitis B or C or cirrhosis
- More often resectable; relatively longer survival time
- Seen most commonly in adolescents and young adults

Quick HIT

The most common malignant liver tumors are HCCs and cholangiocarcinomas. The most common benign liver tumor is the hemangioma.

B. Risk Factors

1. **Cirrhosis**, especially in association with alcohol, NAFLD, or hepatitis B or C; HCC develops in 10% of cirrhotic patients. With chronic HBV infection, HCC can develop without cirrhosis
2. Environmental toxins: aflatoxin, vinyl chloride
3. Genetic susceptibility: AAT deficiency, hemochromatosis, Wilson disease
4. Lifestyle factors: alcohol, cigarette smoking, metabolic disease (NAFLD)
5. Other causes: Schistosomiasis, hepatic adenoma (10% risk of malignant transformation), glycogen storage disease (type 1)

C. Clinical Features

1. Abdominal pain (painful hepatomegaly)
2. Weight loss, anorexia, fatigue
3. Signs and symptoms of chronic liver disease—portal HTN, ascites, jaundice, splenomegaly
4. Paraneoplastic syndromes—erythrocytosis, thrombocytosis, hypercalcemia, carcinoid syndrome, hypertrophic pulmonary osteodystrophy, hypoglycemia, high cholesterol

D. Diagnosis

1. Imaging studies—ultrasound, contrast-enhanced CT, MRI with gadolinium contrast. Typically, CT or MRI can be used to diagnose

HCC noninvasively based on typical appearance.

2. Liver biopsy—usually reserved for equivocal cases. Noninvasive diagnosis by imaging is preferred. Risks include bleeding, pneumothorax, seeding of tumor along needle track, sampling error leading to false negative.
3. Laboratory tests—hepatitis B and C serology, liver function tests (LFTs), coagulation tests.
4. Tumor marker elevation (AFP) may be used in conjunction with imaging test to guide management for suspected HCC. AFP level may be elevated in 40% to 70% of patients with HCC, and is also helpful in monitoring response to therapy.

Quick HIT

Prognosis of HCC

- If unresectable: less than 1 year
- If resectable: 25% of patients are alive at 5 years

Quick HIT

Suspect HCC in a patient with cirrhosis who has a palpable liver mass and elevated AFP level.

E. Treatment

1. Liver resection (in the 10% of patients who have resectable tumors)
2. Liver transplantation if diagnosis is made early
3. If unresectable, consider transcatheter arterial chemoembolization (TACE), radiofrequency ablation, or selective internal radiation therapy. New systemic molecularly targeted agents can be used for advanced disease (e.g., sorafenib)

Nonalcoholic Fatty Liver Disease (NAFLD)

- Spectrum of disease in which hepatic steatosis occurs without excessive alcohol use
- Most common liver disorder in Western industrialized countries
- Ranges from benign disease (NAFLD) to nonalcoholic steatohepatitis (NASH), which can lead to fibrosis and cirrhosis
- Associated with metabolic syndrome: hypertension, obesity, hyperlipidemia, diabetes mellitus, or insulin resistance
- Usually asymptomatic or presents with isolated hepatomegaly unless advanced liver disease has developed
- Typically discovered on routine laboratory tests (mild or moderate elevation in alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) or routine imaging (fatty infiltration of liver)
- Treatment includes alcohol abstinence, weight loss, and modifying cardiovascular risk factors (treat hyperlipidemia, hypertension)

Hemobilia

- Refers to blood draining into the duodenum via the common bile duct (CBD). The source of bleeding can be anywhere along the biliary tract, the liver, or the ampullary region.
- Causes—trauma (most common), papillary thyroid carcinoma, surgery (e.g., cholecystectomy, CBD exploration), tumors, and infection.
- Clinical features—GI bleeding (melena, hematemesis), jaundice, and RUQ pain.
- Endoscopic retrograde cholangiopancreatography (ERCP) is diagnostic. Shows blood coming out of the ampulla of Vater. Angiography may be needed if source of bleeding is not apparent.
- Treatment—supportive care (may require transfusion). If bleeding is severe, surgical resection or arterial embolization is necessary.

Quick HIT

The most common location for liver abscess (both pyogenic and amebic) is the **right** lobe.

Liver Cysts

A. Polycystic Liver Cysts

- Autosomal dominant, usually associated with polycystic kidney disease. Polycystic kidney disease often results in renal failure and is the main determinant of prognosis, whereas liver cysts **rarely** lead to hepatic fibrosis and liver failure.
- Usually asymptomatic; some patients have abdominal pain and upper abdominal mass.
- Treatment is unnecessary in most cases.

B. Echinococcal (Hydatid) Liver Cysts

- Caused by infection from the tapeworm *Echinococcus granulosus* or, less commonly, *Echinococcus multilocularis.* Cysts most commonly occur in the right lobe of the liver.
- Small cysts are asymptomatic; larger cysts may cause RUQ pain and rupture into the peritoneal cavity, causing fatal anaphylactic shock.
- Treatment is surgical resection or aspiration (caution to avoid spilling contents of the cyst into the peritoneal cavity). Albendazole is given after surgery.

Liver Abscess

A. Pyogenic Liver Abscess

- Most common cause is biliary tract obstruction—obstruction of bile flow allows bacterial proliferation. Other causes include GI infection (e.g., diverticulitis, appendicitis), with spread via portal venous system, and penetrating liver trauma (e.g., gunshot wound, surgery).

- Causative organisms include *E. coli, Klebsiella, Proteus, Enterococcus,* and anaerobes.
- Clinical features include fever, malaise, anorexia, weight loss, nausea, vomiting, RUQ pain, and jaundice. Patients appear quite ill.
- Diagnosed by blood cultures and cultures of abscess aspirate, ultrasound or CT scan; elevated LFTs.
- Fatal if untreated. Treatment (IV antibiotics and percutaneous drainage of abscess) reduces mortality to about 2% to 12%. Surgical drainage is sometimes necessary.

B. Amebic Liver Abscess

- Most common in men (9:1), particularly men who have sex with men. Transmitted through fecal–oral contact.
- Caused by intestinal amebiasis *(Entamoeba histolytica)*—the amoebae reach the liver via the hepatic portal vein.
- Clinical features—fever, RUQ pain, nausea/vomiting, hepatomegaly, diarrhea.
- Serologic testing (immunoglobulin G enzyme immunoassay) establishes diagnosis. LFTs are often elevated. The *Entamoeba histolytica* stool antigen test (detects protozoa in stool) is not sensitive. Imaging studies (ultrasound, CT) identify the abscess, but it is difficult to distinguish from a pyogenic abscess.
- Metronidazole is effective treatment in most cases. Therapeutic aspiration of the abscess (image-guided percutaneous aspiration) may be necessary if the abscess is large (high risk of rupture), or if there is no response to medical therapy.

Quick HIT

Pyogenic and amebic abscesses are potentially life threatening, if not detected early.

Budd–Chiari Syndrome

A. General Characteristics

1. Liver disease caused by occlusion of hepatic venous outflow, which leads to hepatic congestion and subsequent microvascular ischemia.
2. The course is variable, but most cases are indolent, with gradual development of portal HTN and progressive deterioration of liver function.
3. Rarely the disease is severe and leads to acute liver failure, which may be fatal without immediate therapy.

B. Causes—hypercoagulable states, myeloproliferative disorders (e.g., polycythemia vera), pregnancy, chronic inflammatory diseases, infection, various cancers, trauma. Condition is idiopathic in up to 40% of cases.

C. Clinical Features (resemble those of cirrhosis)—hepatomegaly, ascites, abdominal pain (RUQ), jaundice, variceal bleeding.

D. Diagnosis—ultrasound with Doppler. Hepatic venography may be needed if imaging if equivocal; serum ascites albumin gradient >1.1 g/dL.

E. Treatment

1. Medical therapy (e.g., anticoagulation, thrombolytics, diuretics) is usually unsatisfactory.
2. Angioplasty and stenting is eventually necessary in most cases (balloon angioplasty with stent placement in inferior vena cava, portacaval shunts). TIPS may be an option to decompress liver. Surgery may be necessary if minimally invasive approach is not effective.
3. Liver transplantation if decompensated cirrhosis is present.

Quick HIT

Three Major Causes of Jaundice

- Hemolysis
- Liver disease
- Biliary obstruction

Jaundice

A. General Characteristics

1. Yellow coloration of skin, mucous membranes, and sclerae due to overproduction or under clearance of bilirubin (see Figure 3-4, Clinical Pearl 3-4)

CLINICAL PEARL 3-4

Bilirubin Metabolism

- Eighty percent of bilirubin is derived from hemoglobin (RBC breakdown). The rest comes from myoglobin breakdown and liver enzymes.
- Hemoglobin is converted to bilirubin in the spleen. This unconjugated bilirubin circulates in plasma, bound to albumin. This bilirubin–albumin complex is not water soluble; therefore, it is not excreted in urine. In the liver, it dissociates from albumin, and the bilirubin is conjugated and excreted into the intestine, where bacteria act on it to produce urobilinogen and urobilin.
- Therefore, unconjugated hyperbilirubinemia results when there is a defect **before** hepatic uptake. Conjugated hyperbilirubinemia results when there is a defect **after** hepatic uptake.

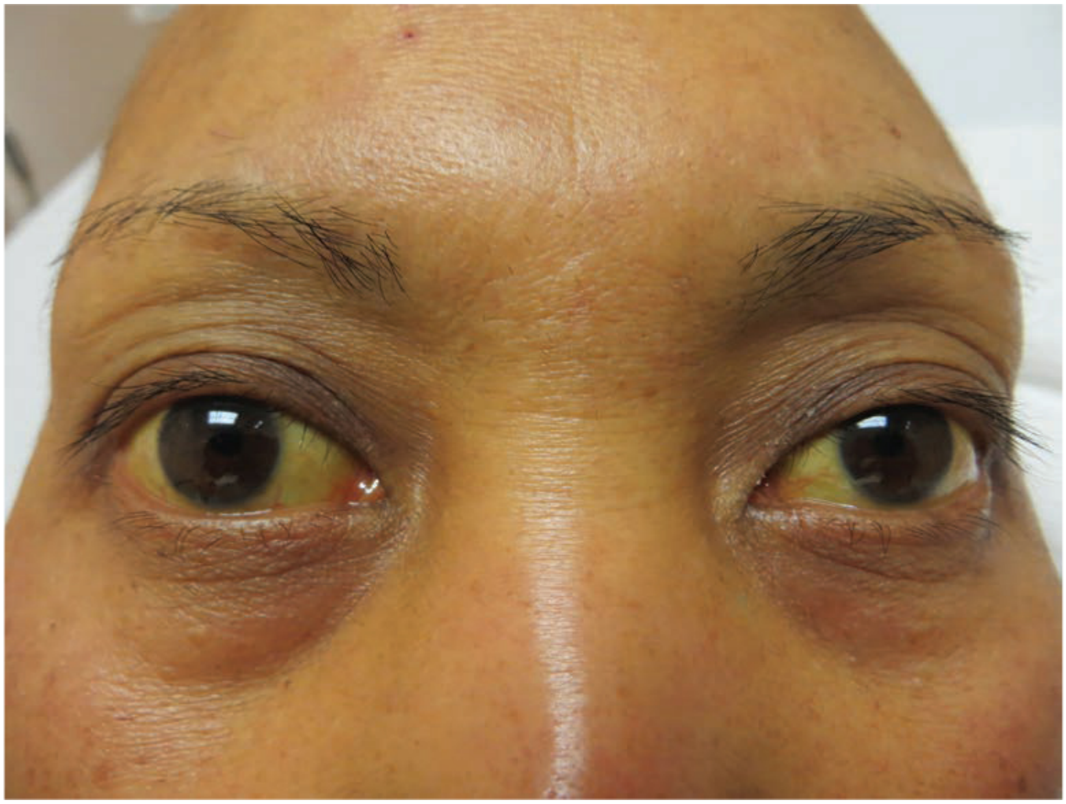


FIGURE 3-4 Jaundice of the skin and scleral icterus.
(Reprinted with permission from Sherman SC, Cico SJ, Nordquist E, et al. *Atlas of Clinical Emergency Medicine*. Wolters Kluwer; 2015:199.)

2. Clinical jaundice usually becomes evident when total bilirubin is >2 to 3 mg/dL
3. Conjugated versus unconjugated bilirubin
   a. Conjugated (direct)
      - Loosely bound to albumin and therefore water soluble
      - When present in excess, it is excreted in urine. **Therefore, dark urine is only seen with conjugated bilirubinemia!**
      - Nontoxic
   b. Unconjugated (indirect)
      - Tightly bound to albumin and therefore not water soluble
      - Cannot be excreted in urine even if blood levels are high
      - Toxic—unbound form can cross blood–brain barrier and cause neurologic deficits

Quick HIT

Dark urine and pale stools signal a diagnosis of conjugated hyperbilirubinemia.

B. Causes

1. **Conjugated (direct) hyperbilirubinemia—urine positive for bilirubin** (see also Clinical Pearl 3-5)
   a. Decreased intrahepatic excretion of bilirubin
      - Hepatocellular disease (viral or alcoholic hepatitis, cirrhosis)
      - Inherited disorders **(Dubin–Johnson syndrome, Rotor syndrome)**
      - Drug-induced (oral contraceptives)
      - Cholestasis of pregnancy
      - PBC
      - Primary sclerosing cholangitis (PSC)

   b. Extrahepatic biliary obstruction
      - Gallstones
      - Carcinoma of head of the pancreas
      - Cholangiocarcinoma
      - Periampullary tumors
      - Extrahepatic biliary atresia

CLINICAL PEARL 3-5

Cholestasis

- This refers to blockage of bile flow (whether intra- or extrahepatic) with a resultant increase in conjugated bilirubin levels.
- Clinical findings
  - Jaundice, gray stools, dark urine
  - Pruritus (bile salt deposition in skin)
  - Elevated serum alkaline phosphatase
  - Elevated serum cholesterol (impaired excretion)
  - Skin xanthomas (local accumulation of cholesterol)
  - Malabsorption of fats and fat-soluble vitamins

2. **Unconjugated (indirect) hyperbilirubinemia—urine negative for bilirubin**
   a. Excess production of bilirubin—hemolytic anemias, Wilson disease
   b. Reduced hepatic uptake of bilirubin or impaired conjugation
      - **Gilbert syndrome**
      - Occurs in up to 7% of the population—autosomal recessive condition in which there is decreased hepatic uridine diphosphate (UDP) glucuronyl transferase activity.
      - Common cause of isolated elevation of unconjugated bilirubin.
      - Exacerbated by stress (e.g., fasting, fever, alcohol, and infection).
      - Asymptomatic in most cases, but occasionally mild jaundice may be present.
      - If history consistent with Gilbert syndrome (unconjugated hyperbilirubinemia during times of stress), no further workup or treatment is necessary
      - Drugs (e.g., sulfonamides, penicillin, rifampin, radiocontrast agents)
      - **Crigler–Najjar syndrome**
      - Type 1—Complete absence of UDP-glucuronosyltransferase in hepatic tissue. Severe unconjugated bilirubinemia, often resulting in brain damage at birth.
      - Type 2—Reduced UDP-glucuronosyltransferase activity, but can be detected in hepatic tissue. Not as severe as type 1.
      - Physiologic jaundice of the newborn (immaturity of conjugating system)
      - Diffuse liver disease (hepatitis, cirrhosis)

***Quick* HIT**

If there is no hemolysis, isolated unconjugated hyperbilirubinemia may indicate Gilbert syndrome, which is usually asymptomatic.

C. Diagnosis

1. Serum levels of total and fractionated (direct and indirect) bilirubin (Figure 3-5).

2. If unconjugated hyperbilirubinemia: CBC, reticulocyte count, haptoglobin, LDH, and peripheral smear may aid in diagnosis of hemolysis as the cause of jaundice.
3. If conjugated hyperbilirubinemia, hepatic panel may point to the cause.
4. Ultrasound (or CT scan) to assess biliary tract for obstruction or anatomic changes.
5. Additional tests (e.g., ERCP, magnetic resonance cholangiopancreatography [MRCP], or percutaneous transhepatic cholangiography [PTC])—depending on the findings of the above tests.
6. Liver biopsy may be indicated in some cases to determine cause of hepatocellular injury.

Quick HIT

- ALT is primarily found in the liver.
- AST is found in many tissues (e.g., heart, skeletal muscle, kidney, brain, others).

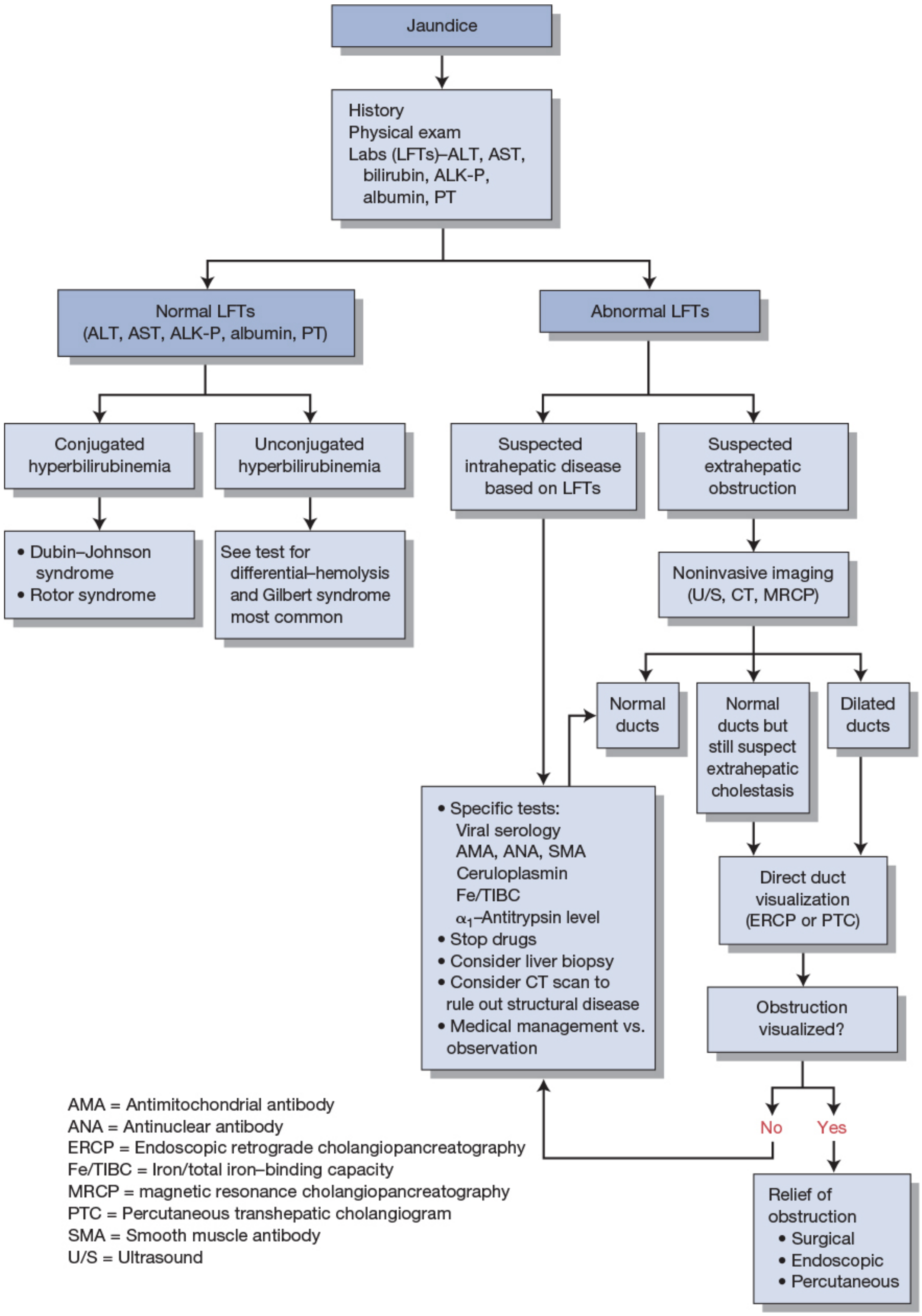
D. Treatment

1. Treat the underlying cause.

Liver Lab Tests

A. Aminotransferases (ALT and AST)

1. ALT is more sensitive and specific than AST for liver damage.
2. ALT and AST usually have a similar increase. The exception is in alcoholic hepatitis, in which the AST–ALT ratio may be >2:1.



AMA = Antimitochondrial antibody
ANA = Antinuclear antibody
ERCP = Endoscopic retrograde cholangiopancreatography
Fe/TIBC = Iron/total iron–binding capacity
MRCP = magnetic resonance cholangiopancreatography
PTC = Percutaneous transhepatic cholangiogram
SMA = Smooth muscle antibody
U/S = Ultrasound

FIGURE 3-5 **Evaluation of jaundice.**

3. If ALT and AST levels are **mildly elevated** (low hundreds), think of NAFLD, alcoholic hepatitis, chronic viral hepatitis, congestive hepatopathy, or medications or supplements.
4. If ALT and AST levels are **moderately elevated** (high hundreds to thousands), think of acute viral hepatitis or drug-induced liver injury.
5. If ALT and AST levels are **severely elevated** (>10,000), extensive hepatic necrosis has occurred. Typical cases are:
   a. Ischemia, shock liver (prolonged hypotension or circulatory collapse)
   b. Acetaminophen toxicity or idiosyncratic drug reaction
   c. Severe viral hepatitis
6. Note that liver transaminases are often normal or even low in patients with cirrhosis (without any active cell necrosis) or metastatic liver disease, because the number of healthy functioning hepatocytes is markedly reduced
7. The following can cause an elevation in ALT or AST levels in asymptomatic patients (note the mnemonic):
   a. **A**utoimmune hepatitis
   b. Hepatitis **B**
   c. Hepatitis **C**
   d. **D**rugs or toxins
   e. **E**thanol
   f. **F**atty liver
   g. **G**rowths (tumors)
   h. **H**emodynamic disorders (e.g., CHF)
   i. **I**ron (hemochromatosis), copper (Wilson disease), or AAT deficiency

***Quick* HIT**

- In alcoholic hepatitis, the AST level is almost always <500, and the ALT level is usually <300.
- Typically AST:ALT ratio ≥2.

Quick HIT

Liver Lab Pearls

- Cholestatic pattern: markedly elevated alkaline phosphatase and GGT; ALT and AST are slightly elevated
- Hepatocellular injury pattern: normal or slightly elevated alkaline phosphatase; markedly elevated ALT and AST

B. Alkaline Phosphatase (ALK-P): Not specific to liver—also found in bone, gut, and placenta.

1. ALK-P is elevated when there is obstruction to bile flow (e.g., cholestasis) in any part of the biliary tree. Normal levels make cholestasis unlikely.
2. If levels are **very high** (≥4 times upper limit of normal), think of extrahepatic biliary tract obstruction or intrahepatic cholestasis (e.g., PBC or drug-induced cirrhosis).
3. If levels are **elevated**, measure the gamma-glutamyl-transferase (GGT) level to make sure the elevation is hepatic in origin (rather than bone or intestinal). If the GGT level is also elevated, this strongly suggests a hepatic origin. If the GGT level is normal but ALK-P is elevated, consider pregnancy or bone disease.

C. Bilirubin (see Jaundice section)

D. GGT is often used to confirm that the ALK-P elevation is of hepatic origin (see above).

E. Albumin—decreased in chronic liver disease, nephrotic syndrome, malnutrition, and is a negative acute phase reactant so can be markedly decreased inflammatory states (e.g., burns, sepsis, trauma).

F. Prothrombin Time (PT)

1. The liver synthesizes clotting factors I, II, V, VII, IX, X, XII, and XIII, the function of which is reflected by PT.
2. PT is not prolonged until most of the liver's synthetic capacity is lost, which corresponds to advanced liver disease.

3. Degree of PT prolongation does not accurately represent coagulation status or bleeding risk in cirrhosis. Other factors in hemostasis are dysregulated, so patients with prolonged PT may be at risk of bleeding or clotting, or both.

Diseases of the Gallbladder and Biliary Tract

Cholelithiasis

A. General Characteristics

1. Cholelithiasis refers to stones in the gallbladder (i.e., gallstones).
2. Types of stones
   a. Cholesterol stones (yellow to green)—associated with the following:
      - Obesity, diabetes, hyperlipidemia
      - Multiple pregnancies, estrogen therapy
      - Crohn disease, ileal resection
      - Advanced age
      - Whitei and Native American ancestry (higher prevalence)
      - Cirrhosis
      - Cystic fibrosis

   b. Pigment stones (brown or black)
      - Black stones are usually found in the gallbladder and are associated with either **hemolysis** (e.g., sickle cell disease, thalassemia, hereditary spherocytosis, artificial cardiac valves) or **alcoholic cirrhosis.**
      - Brown stones are usually found in bile ducts and are associated with biliary tract infection.

   c. Mixed stones have components of both cholesterol and pigment stones, and account for the majority of stones.

Quick HIT

Cholestasis refers to obstruction of bile flow from any cause. If hepatic labs reveal cholestasis, obtain an abdominal or RUQ ultrasound.

B. Clinical Features

1. Most cases are asymptomatic. Majority of patients found to have incidental gallstones will remain asymptomatic.
2. Biliary colic is the cardinal symptom of gallstones and is due to temporary obstruction of the cystic duct by a gallstone. Pain occurs as the gallbladder contracts against this obstruction.
   a. Pain is typically located in the RUQ or epigastrium and may be mild, moderate, or severe.
   b. Patients classically report pain after eating and at night.
   c. *Boas sign*—referred right subscapular pain of biliary colic.

Quick HIT

Once patients with gallstones develop biliary colic, the risk of a complication like cholecystitis is 2% per year.

Quick HIT

Pain in acute cholecystitis is secondary to gallbladder wall inflammation, whereas the pain of biliary colic is secondary to the contraction of the gallbladder against the obstructed cystic duct. Also, the pain of acute cholecystitis persists for several days, whereas the pain of biliary colic lasts only a few hours.

C. Complications

1. Cholecystitis (chronic or acute) with prolonged obstruction of cystic duct
2. Choledocholithiasis with its associated complications—see below
3. Gallstone pancreatitis
4. Gallstone ileus

5. Malignancy

D. Diagnosis

1. RUQ ultrasound has high sensitivity and specificity (>95%) for stones >2 mm.
2. CT scan and MRI are alternatives.

E. Treatment

1. No treatment if the patient is asymptomatic.
2. Elective cholecystectomy for patients with biliary colic.

Quick HIT

Signs of Biliary Tract Obstruction

- Elevated alkaline phosphatase, increased GGT
- Elevated conjugated bilirubin
- Jaundice
- Pruritus
- Clay-colored stools
- Dark urine

Acute Cholecystitis

A. General Characteristics

1. Obstruction of the cystic duct (**not** infection) induces acute inflammation of the gallbladder wall.
2. Chronic cholecystitis may develop with recurrent bouts of acute cholecystitis.
3. Ten percent of patients with gallstones develop acute cholecystitis.

B. Clinical Features

1. Symptoms
   a. RUQ or epigastric pain; pain may radiate to the right shoulder or scapula
   b. Nausea and vomiting, anorexia

2. Signs
   a. RUQ tenderness, rebound tenderness in RUQ
   b. *Murphy sign*: inspiratory arrest during deep palpation of the RUQ
   c. Hypoactive bowel sounds
   d. Fever, leukocytosis

Quick HIT

Acute cholecystitis is a syndrome of RUQ pain, fever, and leukocytosis associated with gallbladder inflammation.

C. Diagnosis

1. RUQ ultrasound is the test of choice.
   a. High sensitivity and specificity
   b. Findings include thickened gallbladder wall, pericholecystic fluid, distended gallbladder, sonographic *Murphy* sign (abdominal tenderness from pressure of ultrasound probe over gallbladder), and presence of stone(s).
2. CT scan is useful for identifying complications of acute cholecystitis (e.g., perforation, abscess, pancreatitis, bowel obstruction)
3. Cholescintigraphy (hepatoiminodiacetic acid [HIDA scan])
   a. Used when ultrasound is inconclusive. Its sensitivity and specificity parallel that of ultrasound. If HIDA scan is normal, acute cholecystitis can be ruled out.
   b. A positive HIDA scan means the gallbladder is not visualized.
   c. If gallbladder is not visualized 60 minutes after injection, diagnosis of acute cholecystitis is confirmed.
4. MRCP may be done to evaluate for suspected concurrent choledocholithiasis (gallstone in CBD)

Quick HIT

Complications of Cholecystitis

- Gangrenous cholecystitis
- Perforation of gallbladder
- Emphysematous cholecystitis
- Biliary-enteric fistula with gallstone ileus
- Empyema of gallbladder

D. Treatment

1. Patient should be admitted. Conservative measures include hydration with IV fluids, bowel rest (NPO), IV antibiotics, analgesics, correction of electrolyte abnormalities.
2. Surgery—cholecystectomy is indicated in most patients with symptomatic gallstones. Cholecystectomy is often done during same hospitalization (patients with high surgical risk may undergo delayed cholecystectomy). Recurrence rate with nonsurgical treatment is as high as 70%. In most patients, early cholecystectomy is preferred.
3. In critically ill patients with high surgical risk, percutaneous cholecystostomy tube placement for drainage of the gallbladder is an alternative to immediate surgery.

Quick HIT

Gallstone Ileus

- Gallstone enters bowel lumen via biliary-enteric fistula—gets "stuck" in terminal ileum and causes obstruction.
- Accounts for less than 1% of mechanical bowel obstructions.

Quick HIT

Complications of acute cholecystitis include gangrene and gallbladder perforation, which can be life threatening.

A 34-year-old man presents to the physician with right upper quadrant pain that has progressed over the last 24 hours. He describes the pain as “stabbing” and radiating to his right scapular region. He has vomited two times. He has no significant medical history, but reports drinking up to 8 beers on the weekends. He has a temperature of 38.6°C, blood pressure of 118/80 mmHg, heart rate of 82 beats per minute, and a respiratory rate of 20 breaths per minute. Physical examination shows severe right upper quadrant pain on deep palpation, most pronounced on palpation after deep inspiration. Laboratory results reveal the following.

Aspartate aminotransferase	51 U/L
Alanine aminotransferase	48 U/L
Alkaline phosphatase	70 U/L
Total bilirubin	1.4 mg/dL
Direct bilirubin	0.7 mg/dL
Amylase	96 U/L
Leukocyte count	18,000/mm^3

Which of the following is contributing to this patient’s disorder?

A. Alcoholic liver disease
B. Gallstone obstruction in the cystic duct
C. Obstruction from carcinoma of the head of the pancreas
D. Gallstone obstruction in the common bile duct

- **The answer is B: Gallstone obstruction in the cystic duct.** The patient in this question is presenting with acute cholecystitis. He is presenting with fever, right upper quadrant pain after a meal that radiates to the right scapula, and positive Murphy sign (pain on

palpation in the right upper quadrant with cessation of inspiration). Additional nonspecific findings include vomiting, leukocytosis, and mild elevation in transaminases. Acute cholecystitis usually arises from gallstone formation that obstructs the cystic duct. **(D)** There is no significant elevation in alkaline phosphatase or bilirubin to suggest a biliary obstruction. **(C)** Similar to common bile duct obstruction, obstruction from a carcinoma of the head of the pancreas would cause elevated alkaline phosphatase levels and would normally present with weight loss and painless jaundice. (**A**) Alcoholic hepatitis presents with modestly elevated transaminases with AST>ALT and often an elevated bilirubin.

Acalculous Cholecystitis

- Acute cholecystitis without stones obstructing the cystic duct (up to 10% of patients with acute cholecystitis).
- Usually idiopathic and seen in patients with severe underlying illness; possibly associated with sepsis, ischemia, burns, severe trauma, and a postoperative state.
- Signs and symptoms are the same as for acute cholecystitis.
- Diagnosis may be difficult because patients with this condition are often severely ill and have other medical problems; so clinical features are less apparent.
- Emergent cholecystectomy is the treatment of choice. For patients who are too ill for surgery, perform percutaneous drainage of the gallbladder with cholecystostomy.

***Quick* HIT**

Complications of CBD Stones

- Cholangitis
- Obstructive jaundice
- Acute pancreatitis
- Biliary colic
- Biliary cirrhosis

Choledocholithiasis

A. General Characteristics

1. Refers to gallstones in the CBD (see Table 3-2)
2. Primary versus secondary stones
   a. Primary stones originate in the CBD due to bile stasis (usually pigmented stones)
   b. Secondary stones originate in the gallbladder and then pass into the CBD (usually cholesterol or mixed stones). These account for 95% of all cases

B. Clinical Features

1. Most patients are symptomatic.
2. Symptoms include RUQ or epigastric pain, nausea, vomiting, and jaundice.

C. Diagnosis

1. Laboratory tests—cholestatic pattern with elevated bilirubin and ALK-P. Transaminases (ALT, AST) may also be elevated early in course.
2. RUQ ultrasound is usually the initial study, but is not a sensitive study for choledocholithiasis. It detects CBD in only 50% of cases, so it cannot be used to rule out this diagnosis.
3. **MRCP** may be done before ERCP to confirm diagnosis prior to more invasive ERCP.
4. **ERCP** is the gold standard (sensitivity and specificity of 95%) and is both diagnostic and therapeutic (see below). Risk of post-ERCP pancreatitis.

***Quick* HIT**

The **onset of symptoms** in **choledocholithiasis** can signal the development of **life-threatening** complications such as cholangitis and acute pancreatitis.

Quick HIT

Do the following in patients with cholangitis:
- Blood cultures
- Supportive care: IV fluids, pain control
- IV antibiotics after blood cultures obtained
- Decompress CBD when patient stable

D. Treatment

1. ERCP with sphincterotomy and stone extraction with stent placement (successful in 90% of patients)
2. Laparoscopic cholecystectomy with intraoperative CBD exploration (in selected cases)

TABLE 3-2 Cholelithiasis Versus Choledocholithiasis

	Cholelithiasis	Choledocholithiasis
Abnormality	Stone in gallbladder	Stone in CBD
Clinical features	Asymptomatic; biliary colic	Asymptomatic, RUQ/epigastric pain, jaundice
Complications	Cholecystitis, choledocholithiasis, gallstone ileus, malignancy	Cholangitis, obstructive jaundice, acute pancreatitis, biliary cirrhosis
Diagnosis	RUQ ultrasound is highly sensitive	MRCP/ERCP is the test of choice; RUQ ultrasound is not sensitive
Treatment	No treatment if asymptomatic; elective cholecystectomy if symptomatic or recurrent	Removal of stone via ERCP and sphincterotomy

Cholangitis

A. General Characteristics

1. Infection of biliary tract secondary to obstruction, which leads to biliary stasis and bacterial overgrowth.
   a. Choledocholithiasis accounts for 60% of cases.

b. Other causes include pancreatic and biliary neoplasm, biliary stricture, invasive procedures such as ERCP, and choledochal cysts.

2. Cholangitis is potentially life threatening and requires emergency treatment.

B. Clinical Features

1. *Charcot triad:* RUQ pain, jaundice, and fever—this classic triad is present in only 50% to 70% of cases.
2. *Reynolds pentad:* Charcot triad plus shock and altered mental status.
3. Patient is acutely ill, and abdominal symptoms may be lacking or may go unrecognized.

Quick HIT

Reynolds pentad is a highly toxic state that requires emergency treatment. **It can be rapidly fatal.**

C. Diagnosis

1. RUQ ultrasound is the initial study.
2. Laboratory findings—hyperbilirubinemia, leukocytosis, mild elevation in serum transaminases. Blood cultures should be done to guide antibiotic therapy.
3. MRCP may be used if diagnosis is unclear with ultrasound.
4. ERCP is the definitive test, but it should not be performed during the acute phase of illness. Once cholangitis resolves, proceed with ERCP to identify the underlying problem and plan treatment.

Quick HIT

RUQ ultrasound is very accurate in detecting gallstones and biliary tract dilatation, but not very accurate in detecting CBD stones.

D. Treatment

1. IV antibiotics and IV fluids

a. Close monitoring of hemodynamics, BP, electrolytes, and urine output is important.
b. Most patients respond rapidly. Once the patient has been afebrile for 48 hours, ERCP can be performed for evaluation of the underlying condition.

2. Decompress CBD via ERCP with sphincterotomy, PTC, or surgical drainage (open or laparoscopic CBD exploration with T-tube insertion) once the patient is stabilized, or emergently if the condition does not respond to antibiotics.

Quick HIT

Septic shock and multiorgan failure are dreaded complications of acute cholangitis with a high mortality rate.

Carcinoma of the Gallbladder

- Most are adenocarcinomas and typically occur in the elderly.
- Associated with gallstones in most cases; other risk factors include biliary-enteric fistula, PSC, and porcelain gallbladder (Figure 3-6).
- Clinical features are nonspecific and suggest extrahepatic bile duct obstruction: jaundice, biliary colic, weight loss, anorexia, and RUQ mass. Palpable gallbladder (Courvoisier sign) is a sign of advanced disease. Early disease is often asymptomatic.

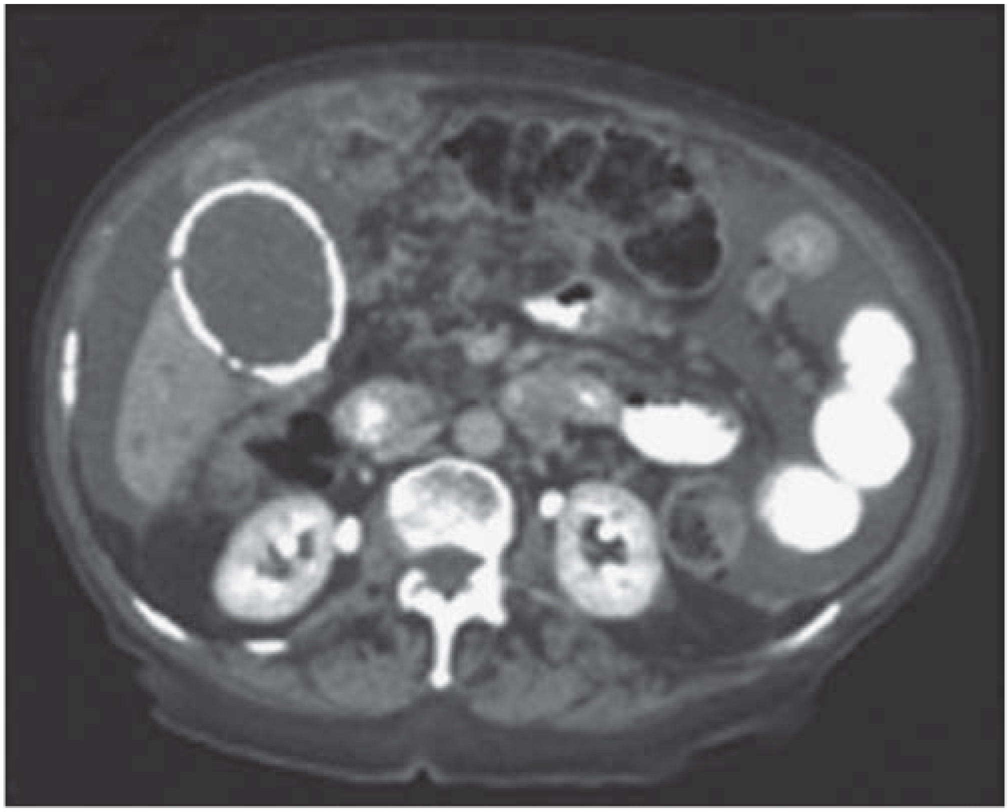


FIGURE 3-6 Porcelain gallbladder. Note the thin layer of mineralization surrounding the gallbladder wall.
(Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 12409.)

- Difficult to remove with surgery: cholecystectomy versus radical cholecystectomy (with wedge resection of liver and lymph node dissection) depending on depth of invasion.
- Prognosis is dismal—more than 90% of patients die of advanced disease within 1 year of diagnosis. Disease often goes undetected until it is advanced.

Quick HIT

Porcelain Gallbladder

- Definition: intramural calcification of the gallbladder wall.
- Prophylactic cholecystectomy is often recommended if symptomatic, or if low surgical risk, due to elevated risk of gallbladder cancer.

Quick HIT

Complications of PSC

- Fat-soluble vitamin deficiencies
- Cholangiocarcinoma (10% to 15% lifetime risk)
- Cholangitis and cholelithiasis
- Can progress to secondary biliary cirrhosis, portal HTN, and liver failure

Primary Sclerosing Cholangitis

A. General Characteristics

1. A chronic idiopathic progressive disease of intrahepatic and/or extrahepatic bile ducts characterized by thickening of bile duct walls and narrowing of their lumens; leads to cirrhosis, portal hypertension, and liver failure (Table 3-3).
2. There is a strong association with UC (less so with Crohn disease). UC is present in up to 90% of patients with PSC; often the UC may dominate the clinical picture. (Note: The course of PSC is unaffected by a colectomy done for UC.)

B. Clinical Features

1. Signs and symptoms begin insidiously.
2. Chronic cholestasis findings, including jaundice and pruritus; all patients eventually present with chronic obstructive jaundice.
3. Other symptoms: fatigue, malaise, weight loss.

C. Diagnosis

1. Cholangiography showing multifocal structuring and bead-like dilatations of intra- and extrahepatic ducts. MRCP, ERCP, and PTC are options. MRCP is noninvasive so is often the first test of choice.
2. Laboratory tests show cholestatic LFTs.

D. Treatment

1. There is no curative treatment other than liver transplantation.

2. When a dominant stricture causes cholestasis, ERCP with stent placement for biliary drainage and bile duct dilatation may relieve symptoms.
3. Many immunosuppressive and antiinflammatory agents have been studied, but none show consistent benefit in slowing disease progression.

TABLE 3-3 Primary Biliary Cholangitis Versus Primary Sclerosing Cholangitis

	Primary Biliary Cholangitis	Primary Sclerosing Cholangitis
Pathology	Intrahepatic bile duct destruction	Intra- and extrahepatic bile duct thickening and lumenal narrowing
Demographics	Female > male 9:1	Male > female
Association with inflammatory bowel disease	None	Strong association with ulcerative colitis (UC) and also Crohn disease
Diagnosis	+ antimitochondrial antibodies (AMAs) in 90–95% of patients. MRCP to exclude other causes. Liver biopsy may be needed.	MRCP or ERCP will show bead-like dilations in intra- and extrahepatic bile ducts
Treatment	Ursodeoxycholic acid slows progression, liver transplantation	Liver transplantation

Primary Biliary Cholangitis

A. General Characteristics

1. PBC is a chronic and progressive cholestatic liver disease characterized by **destruction of intrahepatic bile ducts** with portal inflammation and scarring (Table 3-3).
2. It is a slowly progressive disease with a variable course. It may progress to cirrhosis and end-stage liver failure.
3. It is an **autoimmune disease** that is often associated with other autoimmune disorders.

4. It is most common in **middle-aged women.**

Quick HIT

Etiology of Secondary Biliary Cirrhosis. This disease occurs in response to chronic biliary obstruction from the following:

- Long-standing mechanical obstruction
- Sclerosing cholangitis
- Cystic fibrosis
- Biliary atresia

B. Clinical Features

1. Fatigue
2. Pruritus (early in course of disease)
3. Jaundice (late in course of disease)
4. RUQ discomfort
5. Xanthomata and xanthelasmata
6. Osteoporosis
7. Portal HTN (with resultant sequelae)

C. Diagnosis

1. Laboratory findings
   a. Cholestatic pattern on hepatic labs (elevated ALK-P)
   b. **Positive antimitochondrial antibodies (AMAs) found in 90% to 95% of patients.** This is the hallmark of the disease
   c. Elevated cholesterol, HDL
   d. Elevated immunoglobulin M
2. Liver biopsy (percutaneous or laparoscopic) to confirm the diagnosis. Biopsy may not be necessary if all typical features are present: positive AMA, elevated ALK-P, and clinical picture consistent with PBC
3. Abdominal ultrasound, MRCP, or CT scan to rule out biliary obstruction

D. Treatment

1. Treatment is symptomatic for pruritus (cholestyramine) and osteoporosis (calcium, bisphosphonates, vitamin D).

2. Ursodeoxycholic acid (a hydrophilic bile acid) has been shown to slow progression of the disease.
3. Liver transplantation is the only curative treatment available.

Cholangiocarcinoma

A. General Characteristics

1. Tumor of intra- or extrahepatic bile ducts: most are adenocarcinomas.
2. Most are diagnosed between 50 and 70 years of age
3. Located in three regions: proximal third of the CBD (most common, also called Klatskin tumor), distal extrahepatic (best chance of resectability), intrahepatic (least common)
4. Prognosis is dismal—survival is less than 1 year after diagnosis
5. Risk factors
   a. PSC is the major risk factor in the United States.
   b. Other risk factors include UC, choledochal cysts, and liver fluke infection (*Clonorchis* and *Opisthorchis*, especially in Asia)

Quick HIT

Klatskin Tumors

- Tumors in proximal third of CBD—involve the junction of right and left hepatic ducts.
- Very poor prognosis because recurrence is high after resection.

B. Clinical Features

1. Obstructive jaundice and associated symptoms: dark urine, clay-colored stools, and pruritus
2. Weight loss
3. Dull abdominal pain

C. Diagnosis

1. Cholangiography (MRCP, ERCP, or EUS) for diagnosis and assessment of resectability.

2. If the patient has an unresectable tumor (more likely the case with proximal than distal bile duct tumors), stent placement is an option during either PTC or ERCP and may relieve biliary obstruction.

D. Treatment

1. Most patients do not have resectable tumors at diagnosis.
2. The survival rate is low despite aggressive chemotherapy, stenting, or biliary drainage.

Biliary Cysts

- Cystic dilatations of biliary tree involving either the extra- or intrahepatic ducts, or both; more common in women (4:1).
- Clinical features: epigastric pain, jaundice, fever, and RUQ mass.
- Complications: cholangiocarcinoma (most feared complication—risk is about 20% over 20 years), hepatic abscess, recurrent cholangitis/pancreatitis, rupture, biliary obstruction, cirrhosis, and portal HTN.
- MRCP is the best noninvasive test, and ERCP is definitive for diagnosis.
- Treatment is surgery: complete resection of the cyst with a biliary-enteric anastomosis to restore continuity of biliary system with bowels.

Biliary Stricture

- Most common cause is iatrogenic injury (e.g., prior biliary surgery such as cholecystectomy, liver transplantation). Other causes include recurring choledocholithiasis, chronic pancreatitis, and PSC.
- Clinical features are those of obstructive jaundice.
- Complications can be life threatening: secondary biliary cirrhosis, liver abscess, and ascending cholangitis.
- Treatment involves endoscopic stenting (preferred) or surgical bypass if obstruction is complete or if endoscopic therapy fails.

Biliary Dyskinesia

- Motor dysfunction of the sphincter of Oddi which leads to recurrent episodes of biliary colic without any evidence of gallstones on diagnostic

studies such as ultrasound, CT scan, and ERCP.

- Diagnosis method depends on whether abnormal liver labs and dilated CBD are present. If sphincter of Oddi dysfunction is suspected, manometry may be necessary. Other diagnostic options include biliary provocation testing with CCK administration and HIDA scan or MRCP.
- Treatment options include laparoscopic cholecystectomy and ERCP with sphincterotomy.

Quick HIT

CCK is the hormone that relaxes the sphincter of Oddi and contracts the gallbladder.

Diseases of the Appendix

Acute Appendicitis

A. General Characteristics

1. Pathogenesis
   a. The lumen of the appendix is obstructed by hyperplasia of lymphoid tissue (60% of cases), a fecalith (35% of cases), a foreign body, or other rare causes (parasite or carcinoid tumor [5% of cases]).
   b. Obstruction leads to stasis (of fluid and mucus), which promotes bacterial growth, leading to inflammation.
   c. Distention of the appendix can compromise blood supply. The resulting ischemia can lead to infarction or necrosis if untreated. Necrosis can result in appendiceal perforation, and ultimately peritonitis.
2. Peak incidence is in the teens to mid-20s. Prognosis is far worse in infants and elderly patients (higher rate of perforation).

Quick HIT

Perforation of Appendix

- Complicates up to 20% of cases.
- Risk factors: delay in treatment (>24 hours) and extremes of age.
- Signs of appendiceal rupture (high fever, tachycardia, marked leukocytosis, peritoneal signs, toxic appearance).

B. Clinical Features

1. Symptoms
   a. RLQ abdominal pain—Classically starts in the epigastrium, moves toward umbilicus, and then to the RLQ (although migratory pain only occurs 50% to 60% of the time). With distention of the appendix, the parietal peritoneum may become irritated, leading to sharp pain
   b. Anorexia
   c. Nausea and vomiting (typically follow pain)
2. Signs
   a. Tenderness in RLQ (maximal tenderness at *McBurney point:* two-thirds of the distance from the umbilicus to the right anterior superior iliac spine).
   b. Rebound tenderness, guarding, diminished bowel sounds.
   c. Low-grade fever (may spike if perforation occurs).
   d. *Rovsing sign:* deep palpation in LLQ causes referred pain in RLQ.
   e. *Psoas sign:* RLQ pain when right thigh is extended as the patient lies on the left side.
   f. *Obturator sign:* pain in RLQ when flexed right thigh is internally rotated when patient is supine.

Quick HIT

Acute appendicitis is a clinical diagnosis. Laboratory findings (mild leukocytosis) are only supportive. Radiographs or other imaging studies are unnecessary unless the diagnosis is uncertain or the presentation is atypical.

C. Diagnosis

1. Acute appendicitis is a clinical diagnosis.
2. Laboratory findings (mild leukocytosis) are only supportive.
3. Imaging studies may be helpful if diagnosis uncertain or in atypical presentations.
   a. CT scan (sensitivity 95%)—lowers the false-positive rate significantly.
   b. Ultrasound (sensitivity of 85%).

D. Treatment

1. **Appendectomy** (usually laparoscopic). Up to 20% of patients who are diagnosed with acute appendicitis are found to have a normal appendix during surgery. Because the illness is potentially life threatening, this is an acceptable risk even during pregnancy.
2. Low-risk patients may be considered for medical management alone with antibiotics to avoid surgery. Close follow-up is necessary in case urgent surgery is required.

Quick HIT

Carcinoid syndrome is mostly associated with metastatic neuroendocrine tumors (NETs) in the small intestine or colon.

- Excess serotonin secretion can lead to **carcinoid syndrome**, which is manifested by cutaneous flushing, diarrhea, sweating, wheezing, abdominal pain, and heart valve dysfunction.
- Risk factors of metastasis increase with the size of the tumor. Metastases are rare with appendiceal tumors. Small bowel tumors have the greatest likelihood of malignancy.
- Surgical resection is the treatment of choice. Octreotide can treat symptoms of carcinoid syndrome and is used if tumor is unresectable.

Neuroendocrine Tumors (NETs) and Carcinoid Syndrome

- Carcinoid refers to well-differentiated NETs originating from **neuroendocrine cells** that secrete **serotonin** and other vasoactive substances.

- Most often found in the GI system (small bowel, appendix, colon, rectum, stomach), but can be found anywhere (lung or genitourinary tract).

Diseases of the Pancreas

Acute Pancreatitis

A. General Characteristics

1. There is inflammation of the pancreas resulting from prematurely activated pancreatic digestive enzymes that invoke pancreatic tissue autodigestion.
2. Most patients with acute pancreatitis have mild to moderate disease, but up to 25% have severe disease. There is a spectrum of severity:
   a. Mild acute pancreatitis is most common and responds well to supportive treatment.
   b. Moderately severe or severe acute pancreatitis (necrotizing pancreatitis) has significant morbidity and mortality.

B. Causes

1. Gallstones (40%)—the gallstone passes into the bile duct and blocks the ampulla of Vater, or edema results from passage of stone
2. Alcohol use disorder (30%)
3. Hypertriglyceridemia (serum triglycerides >1000 mg/dL usually)
4. Post-ERCP—pancreatitis occurs in up to 5% of patients undergoing ERCP
5. Genetic risk
6. Medications—sulfonamides, diuretics, estrogens, HIV medications, and many other drugs have been implicated
7. Pancreatic duct injury (blunt trauma, postoperative complications)
8. Idiopathic
9. Rare causes:
   a. Autoimmune pancreatitis
   b. Viral infections (e.g., mumps, Coxsackievirus B)
   c. Scorpion and brown recluse spider bites

d. Pancreas divisum (controversial)
e. Pancreatic cancer
f. Hypercalcemia

Quick HIT

Most cases of acute pancreatitis are due to alcohol or gallstones (70% to 80%). Recurrences are common in alcoholic pancreatitis.

Quick HIT

Causes of acute pancreatitis—I GET SMASHED

I—idiopathic
G—gallstones
E—ethanol
T—trauma
S—steroids
M—mumps / malignancy
A—autoimmune
S—scorpion stings /spider bites
H—hypertriglyceridemia, hypercalcemia
E—ERCP
D—drugs

C. Clinical Features

1. Symptoms
   a. Acute, persistent abdominal pain, usually in the epigastric region
      - May radiate to back (50% of patients)
      - Often steady, dull, and severe; worse when supine and after meals

   b. Nausea and vomiting, anorexia
2. Signs
   a. Low-grade fever, tachycardia, hypotension, hypoxia
   b. Epigastric tenderness, abdominal distention
   c. Decreased or absent bowel sounds indicate ileus
   d. The following signs are seen with hemorrhagic pancreatitis as blood tracks along fascial planes:
      - *Grey Turner sign* (flank ecchymoses)

- *Cullen sign* (periumbilical ecchymoses)
- *Fox sign* (ecchymosis of inguinal ligament)

Quick HIT

The diagnosis of acute pancreatitis is usually made based on clinical presentation in combination with lab findings (elevated serum lipase or amylase). Imaging is supportive.

D. Diagnosis

1. Must fulfill two of three criteria: classical clinical presentation (epigastric pain that radiates to the back), elevated serum lipase or amylase ≥3 times upper limit of normal, and characteristic imaging findings.
2. Laboratory studies
   a. Elevated serum lipase and amylase. Lipase is more specific
   b. Hepatic panel—to identify cause (gallstone pancreatitis)
   c. Hyperglycemia and leukocytosis may also be present
3. Abdominal radiograph
   a. Has a limited role in the diagnosis of acute pancreatitis.
   b. More helpful in ruling out other diagnoses or complications, such as intestinal perforation (free air) or pleural effusion. The presence of calcifications can suggest chronic pancreatitis.
   c. In some cases, one may see a **sentinel loop** (area of air-filled bowel usually in LUQ, which is a sign of localized ileus) or a **colon cut-off sign** (air-filled segment of transverse colon abruptly ending or "cutting off" at the region of pancreatic inflammation).
4. Abdominal ultrasound
   a. Can help in identifying cause of pancreatitis (e.g., gallstones).
   b. Often difficult to visualize pancreas due to overlying bowel gas.
5. CT scan of the abdomen with contrast
   a. Most accurate test for diagnosis of acute pancreatitis and for identifying complications of the disease.
   b. Indicated in patients with severe acute pancreatitis.
6. MRI or MRCP: better at detecting early acute pancreatitis, but difficult to do in critically ill patients due to time required for scan.

7. Indications for ERCP:
   a. Severe gallstone pancreatitis with biliary obstruction.
   b. To identify uncommon causes of acute pancreatitis if disease is recurrent.

Quick HIT

The level of either amylase or lipase does not reliably predict the severity of disease.

Quick HIT

Hypocalcemia that results from acute pancreatitis is due to fat saponification: fat necrosis binds calcium.

Quick HIT

Pseudocysts may be present at sites distant from the pancreas.

E. Complications

1. Pancreatic necrosis (may be sterile or infected)
   a. Sterile pancreatic necrosis—infection may develop, but half of all cases resolve spontaneously. These patients should be monitored closely in an ICU. Prophylactic antibiotics are not recommended
   b. Infected pancreatic necrosis—high rates of multiorgan failure and high mortality rate; surgical debridement and antibiotics are indicated
   c. The only way to distinguish sterile from infected necrosis is via CT-guided percutaneous aspiration with Gram stain/culture of the aspirate
2. Pancreatic pseudocyst
   a. Encapsulated fluid collection that appears usually more than 4 weeks after an acute attack—unlike a true cyst, it lacks an epithelial lining

   b. Complications of untreated pseudocysts include rupture, infection, gastric outlet obstruction, fistula, hemorrhage into cyst, and pancreatic ascites. It may impinge on adjacent abdominal organs (e.g., duodenum, stomach, transverse colon) if large enough; or if located in the head of the pancreas, it may cause compression of the CBD
   c. Diagnosis: CT or MRI is the test of choice
   d. Treatment: depends on presence of symptoms and complications
      - Symptomatic or complications: endoscopic, percutaneous, or surgical drainage
      - Asymptomatic without complications: observe with serial CT or MRI
3. Hemorrhagic pancreatitis
   a. Characterized by Cullen sign, Grey Turner sign, and Fox sign
   b. CT scan with IV contrast is the study of choice
4. Abdominal compartment syndrome
   a. Sustained intraabdominal pressure >20 mmHg with new organ failure
   b. Peripancreatic inflammation combined with aggressive fluid resuscitation, reactive ascites, and ileus can lead to compartment syndrome
   c. Requires monitoring in ICU with urinary bladder pressures and may require surgical decompression
5. Splanchnic venous thrombosis
   a. Diagnosed (often incidentally) with CT
   b. Treat underlying pancreatitis
   c. Start anticoagulation if clot causes bowel ischemia or liver dysfunction
6. Adult respiratory distress syndrome—a life-threatening complication with high mortality rate
7. Pancreatic ascites/pleural effusion—the most common cause is inflammation of peritoneal surfaces
8. Ascending cholangitis—due to gallstone in the ampulla of Vater, leading to infection of biliary tract; see section on cholangitis
9. Pancreatic abscess (rare)—develops over 4 to 6 weeks and is less life threatening than infected pancreatic necrosis

Quick HIT

Most patients with acute pancreatitis respond to supportive care of pain control, nutritional support, IV fluids, and correction of electrolyte abnormalities.

F. Treatment

1. Patients with mild acute pancreatitis:
   a. Initial bowel rest (NPO)—goal is to rest the pancreas while pain control is achieved. Early enteral nutrition is a priority once pain and inflammation is improved. Patient should resume oral diet if able, otherwise start nasojejunal feeding.
   b. IV fluids—patients often have severe intravascular volume depletion. Correct electrolyte abnormalities. Use isotonic crystalloids (lactated Ringer's solution or normal saline) for fluid resuscitation. Lactated Ringer's solution may be superior to normal saline, as normal saline can cause hyperchloremic metabolic acidosis. Acidosis will increase pancreatic zymogen activity which will then worsen autodigestion.
   c. Pain control. Opioids are safe and effective in acute pancreatitis. IV opioids are usually necessary, sometimes in form of patient-controlled analgesia pump. Historically, meperidine was favored over morphine due to concerns that morphine increased sphincter of Oddi pressure. However, no studies have validated this (and meperidine has worse side-effect profile).
   d. All patients with gallstone pancreatitis should have cholecystectomy after recovery from pancreatitis. These patients may benefit from early ERCP.

TABLE 3-4 Bedside Index of Severity in Acute Pancreatitis (BISAP) Score

Criteria	Interpretation
BUN >25 mg/dL (1 point)	0–2 points: lower mortality (<2%) 3–5 points: higher mortality (>15%)
Abnormal mental status with a Glasgow coma score <15 (1 point)	
Evidence of SIRS (1 point)	
Patient age > 60 years (1 point)	
Imaging study reveals pleural effusion (1 point)	

2. Patients with severe pancreatitis:
   a. Admit to the ICU.
   b. Early enteral nutrition in the first 72 hours is recommended through a nasojejunal tube if patient is unable to eat by mouth.
   c. If patient does not tolerate enteral feeding, total parenteral nutrition (TPN) can be used. However, always prioritize enteral nutrition (TPN is associated with increased mortality compared to enteral nutrition alone).
   d. Up to a fifth of patients develop infection (bloodstream infection, pneumonia, UTI). Monitor closely for signs of infection and start antibiotics if concerned.

G. Prognosis

1. There are multiple risk calculators to estimate severity and prognosis.
2. Ranson's criteria was historically used, but is a poor predictor of severity.
3. The Acute Physiology and Chronic Health Examination (APACHE II) score can be helpful in ICU but involves many variables and can be cumbersome.
4. One useful tool is the bedside index of severity in acute pancreatitis (BISAP) score (see Table 3-4—BISAP score).

A 39-year-old woman presents with epigastric pain that has radiated to her back for the last 8 hours. She endorses nausea and vomiting. Her past medical history is significant for hyperlipidemia; however, she does not take any medications other than a multivitamin. She denies alcohol or drug use. On examination, the patient is slightly febrile at 38.4°C, with a blood pressure of 114/83 mmHg, a heart rate of 98 beats per minute, and a respiratory rate of 22 breaths per minute. The patient has decreased bowel sounds and guarding in her epigastrium.

Which of the following results is the most specific finding in this condition?

A. Elevated amylase
B. Elevated ALT
C. Elevated lipase
D. Positive fecal fat test

- **The answer is C: Elevated lipase.** The patient in this question is presenting with signs and symptoms of acute pancreatitis (epigastric abdominal pain radiating to the back, nausea, and vomiting). Lipase has the greatest *specificity* of all possible tests and is usually more elevated than amylase in acute pancreatitis. **(A)** Amylase can sometimes be normal in acute pancreatitis (particularly if the etiology is hyperlipidemia), and is less specific than lipase. **(B)** Elevation in AST and ALT may suggest biliary obstruction (e.g., gallstone pancreatitis), but it is not sensitive or specific for acute pancreatitis. **(D)** Positive fecal fat test is typically positive (>7 g/d) in *chronic* pancreatitis; however, chronic pancreatitis presents with symptoms of malabsorption.

Chronic Pancreatitis

A. General Characteristics

1. Persistent or continuing inflammation of the pancreas, with fibrotic tissue replacing pancreatic parenchyma, and alteration of pancreatic ducts (areas of stricture/dilation); eventually results in irreversible destruction of the pancreas.
2. The endocrine and exocrine functions of the pancreas are impaired.
3. Causes
   a. **Chronic alcohol use disorder is the most common cause (>50% of cases).**
   b. Other causes include idiopathic chronic pancreatitis, hereditary pancreatitis, autoimmune pancreatitis, and recurrent acute pancreatitis.

Quick HIT

The combination of chronic epigastric pain and symptoms of diarrhea, steatorrhea, or weight loss is suspicious for chronic pancreatitis. The classic triad of steatorrhea, diabetes mellitus, and pancreatic calcifications on imaging is also diagnostic.

B. Clinical Features

1. Severe pain in the epigastrium; recurrent or persistent abdominal pain.
   a. Often accompanied by **nausea, vomiting, and anorexia.**
   b. May be aggravated by an episode of heavy alcohol use, or by eating.
   c. Radiates to the back in 50% of cases.
   d. Presence or severity of pain does not correlate with extent of pancreatic damage on imaging
2. Weight loss, due to malabsorption, alcohol abuse, and diabetes; steatorrhea secondary to fat malabsorption.
3. May be asymptomatic. Pancreatic calcifications can be diagnosed incidentally on CT or MRI.

Quick HIT

Chronic pancreatitis presents as chronic unrelenting pain with episodic flare-ups.

C. Diagnosis

1. CT scan (Figure 3-7) or MRI/MRCP are the initial studies of choice. Mild to moderate cases may not be detectable, so a normal CT scan does not necessarily rule out chronic pancreatitis. Repeat imaging over time may be necessary for suspected cases.
2. Abdominal radiograph is less useful as pancreatic calcifications are found in only 30% of cases and can be easily confused with vascular calcifications.
3. Endoscopic ultrasound (EUS) can be done for rare cases, but is invasive. ERCP is no longer done routinely due to associated risks and availability of noninvasive imaging.
4. Laboratory studies can be helpful in diagnosis. Measure pancreatic enzymes in stool (fecal elastase) to determine if exocrine pancreatic insufficiency is present. Direct testing can also be done by administering secretin or CCK to stimulate pancreas and directly sampling duodenal fluid with endoscope. Serum amylase and lipase levels are usually low or normal in chronic pancreatitis, and are not helpful for diagnosis.

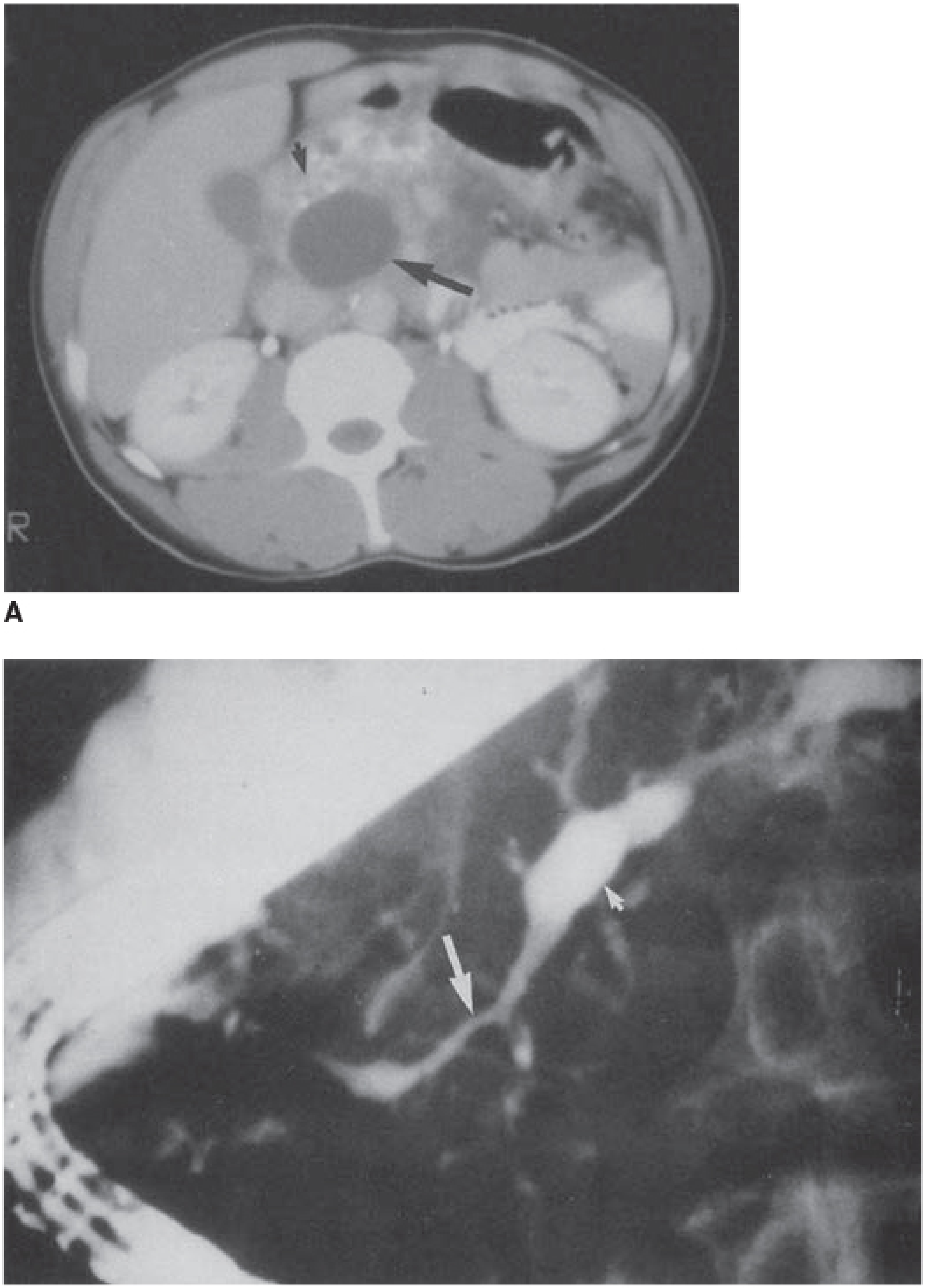
D. Complications

1. Chronic opioid dependence and opioid use disorder can complicate management
2. Diabetes mellitus/impaired glucose tolerance (pancreatic endocrine insufficiency)
   a. Caused by progressive loss of islets of Langerhans
   b. Eventually appears in up to 40% of patients
3. Malabsorption/steatorrhea (pancreatic exocrine insufficiency)
   a. Occurs when pancreatic enzyme secretion decreases significantly, a late manifestation of chronic pancreatitis
   b. May lead to fat-soluble vitamin deficiencies and sequela (e.g., osteoporosis)

4. Pseudocyst formation
5. Pancreatic ductal dilation
6. Biliary obstruction (may occur secondary to fibrosis in head of gland)
7. Splenic vein thrombosis and gastric varices
8. Effusions (e.g., pleural, pericardial, peritoneal)
9. Pancreatic adenocarcinoma—patients with chronic pancreatitis are at increased risk

E. Treatment

1. Nonoperative management
   a. Analgesics (often require opioids). Celiac plexus blockade is an option for refractory pain.
   b. Bowel rest (NPO) during flares
   c. Pancreatic enzyme replacement therapy
      - Reduces fat and fat-soluble vitamin malabsorption, improves steatorrhea
      - H_2-Blockers are needed for non–enteric-coated formulations of pancreatic enzymes to prevent degradation of the pancreatic enzyme supplements by gastric acid.
   d. Insulin—may be necessary due to severe pancreatic endocrine insufficiency.
   e. Cessation of alcohol and smoking
   f. Frequent, small-volume, low-fat meals—may improve abdominal pain.
2. Surgery—main goal is relief of incapacitating abdominal pain.
   a. Endoscopic or surgical drainage of pancreatic duct for those with ductal dilatation
   b. Pancreatic resection (distal pancreatectomy, Whipple procedure)



A

B

FIGURE 3-7 **A: CT scan of chronic pancreatitis. Note the area of calcification (*small arrow*) and a pseudocyst (*large arrow*) in the head of the pancreas. B: Typical findings on ERCP in chronic pancreatitis. Note the areas of stricture (*large arrow*)**

and duct dilatation (*small arrow*) throughout the pancreatic duct. This creates a "chain of lakes" appearance.
(Reprinted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:958. Figures 117.9 and 117.10 respectively.)

Pancreatic Cancer

A. General Characteristics

1. Most common in advanced age (most patients are >60 years old)
2. Anatomic location
   a. Pancreatic head (75% of cases)
   b. Pancreatic body (20% of cases)
   c. Pancreatic tail (5% to 10% of cases)
3. Risk factors
   a. **Cigarette smoking** (most clearly established risk)
   b. Genetic predisposition
   c. Chronic pancreatitis
   d. Diabetes
   e. Heavy alcohol use (controversial)
   f. Exposure to chemicals—benzidine and β-naphthylamine
   g. Association with obesity and physical inactivity
4. The prognosis is poor: most patients die within months of diagnosis

B. Clinical Features

1. Abdominal pain (80% of patients)—may be a vague and dull ache
2. Jaundice
   a. Most common with carcinoma of head of pancreas
   b. May be accompanied by pruritus, dark urine, pale stools
3. Weight loss (common due to decreased food intake and malabsorption); anorexia
4. Recent onset of glucose intolerance, but the diabetes is mild
5. Generalized weakness and fatigue
6. Migratory thrombophlebitis (*Trousseau syndrome*)—develops in 10% of cases

7. *Courvoisier sign* (painless palpable gallbladder)—present in 13% of patients

Quick HIT

Painless jaundice is **not** common in pancreatic cancer!

Quick HIT

The early clinical findings of pancreatic cancer are very vague and nonspecific. By the time a diagnosis is made, most patients have an incurable level of advanced disease.

C. Diagnosis

1. CT scan is the preferred test for diagnosis and assessment of disease spread
2. Abdominal ultrasound is often the first study to workup biliary obstruction but has limited sensitivity for small tumors
3. ERCP is the most sensitive test for diagnosing pancreatic cancer. It can also distinguish cancer of the head of the pancreas from tumors of the CBD, duodenum, ampulla, and lymphomas, which have more favorable prognosis
4. Tumor markers
   a. CA 19-9 (sensitivity and specificity of 70% to 90%). Most valuable as a prognostic indicator and to track disease activity
   b. CEA has less sensitivity and specificity, can also be used for prognostication

D. Treatment

1. Surgical resection (Whipple procedure) is the only hope for a cure; however, only a minority of tumors are resectable (roughly 15% to 20%). **The prognosis is poor even after resection, with a 5-year survival rate of 10%.**
2. Palliative chemotherapy or immunotherapy is often given for unresectable disease.

3. If the tumor is unresectable and biliary obstruction is present, perform ERCP with stent placement across the obstruction for palliation.

Quick HIT

Aortoenteric Fistula is a rare but lethal cause of GI bleeding. The classic presentation is a patient with a history (sometimes distant) of aortic graft surgery who has a small GI bleed involving the duodenum before massive, fatal hemorrhage hours to weeks later. Perform surgery during this small window of opportunity to prevent death.

Gastrointestinal Bleeding

A. General Characteristics

1. Upper GI bleeding refers to a source of bleeding above the ligament of Treitz in the duodenum.
2. Lower GI bleeding is classically defined as bleeding below the ligament of Treitz.

B. Causes

1. Upper GI bleeding
   a. Peptic ulcer disease (PUD)—duodenal ulcer, gastric ulcer (risk factors include *Helicobacter pylori* infection, NSAIDs, stress, or excess gastric acid)
   b. Esophagitis
   c. Gastritis, duodenitis
   d. Sequelae of portal hypertension: esophageal or gastric varices, portal hypertensive gastropathy, gastric antral vascular ectasia (GAVE)
   e. Mallory–Weiss tear
   f. Angiodysplasias or arteriovenous malformations (AVMs)
   g. Dieulafoy vascular malformation—submucosal dilated arterial lesions that can cause massive GI bleeding
   h. Malignancy
   i. Hemobilia or hemosuccus pancreaticus (rare)

j. Aortoenteric fistulas (rare, usually iatrogenic, ask about prior aortic aneurysm/graft)

2. Lower GI bleeding
   a. Diverticulosis (up to 50% of cases)—most common source of GI bleeding in adults
   b. Angiodysplasia
   c. Hemorrhoids and anal fissures
   d. Ischemic colitis
   e. Colorectal cancer or polyps
   f. IBD (UC, Crohn disease)
   g. Postpolypectomy
   h. Radiation colitis
   i. Infectious colitis
   j. Small intestinal bleeding—diagnosed by excluding upper GI and colonic bleeding

Quick HIT

A lower GI bleed in patients over 40 is colon cancer until proven otherwise.

Quick HIT

Most cases of GI bleeding stop spontaneously with supportive therapy.

Quick HIT

- Bleeding from the small bowel may manifest as melena or hematochezia.
- Colonic sources of bleeding present with either occult blood in the stool or hematochezia.

C. Clinical Features

1. Type of bleeding:
   a. Hematemesis—vomiting blood; suggests upper GI bleeding. Indicates moderate to severe bleeding that may be ongoing.

b. “Coffee grounds” emesis—suggests upper GI bleeding as well as a **lower rate of bleeding** (enough time for vomitus to transform into “coffee grounds”).

c. Melena—black, tarry, liquid, foul-smelling stool.
- Caused by degradation of hemoglobin by bacteria in the colon; presence of melena indicates that blood has remained in GI tract for several hours.
- The further the bleeding site is from the rectum, the more likely melena will occur.
- **Note that dark stools can also result from bismuth, iron, spinach, charcoal, and licorice.**
- Melena suggests upper GI bleeding 90% of the time. Occasionally, the jejunum or ileum is the source. It is unusual for melena to be caused by a colonic lesion, but if it is, the ascending colon is the most likely site.

d. Hematochezia—bright red blood per rectum.
- This usually represents a lower GI source (typically **left colon** or **rectum**). Consider diverticulosis, arteriovenous malformations, hemorrhoids, and colon cancers.
- It may result from massive upper GI bleeding that is bleeding very briskly (so that blood does not remain in colon to turn into melena —see above). This often indicates heavy bleeding, and patient often has some degree of hemodynamic instability. An upper GI source is present in about 5% to 10% of patients with hematochezia.
- Occult blood in stool—source of bleeding may be anywhere along GI tract.

2. Signs of volume depletion (depending on rate and severity of blood loss).
3. Symptoms and signs of anemia (e.g., fatigue, pallor, exertional dyspnea).

Quick HIT

Always ask patients with GI bleeding if they took any NSAIDs, antiplatelet agents (e.g., aspirin, clopidogrel), or anticoagulants.

Quick HIT

Hematemesis and melena are the most common presentations of acute upper GI bleed, and patients may have both symptoms. Occasionally, a brisk upper GI bleed presents as hematochezia.

Quick HIT

An elevated PT may be indicative of liver dysfunction, vitamin K deficiency, coagulation factor deficiency, a consumptive coagulopathy, or warfarin therapy.

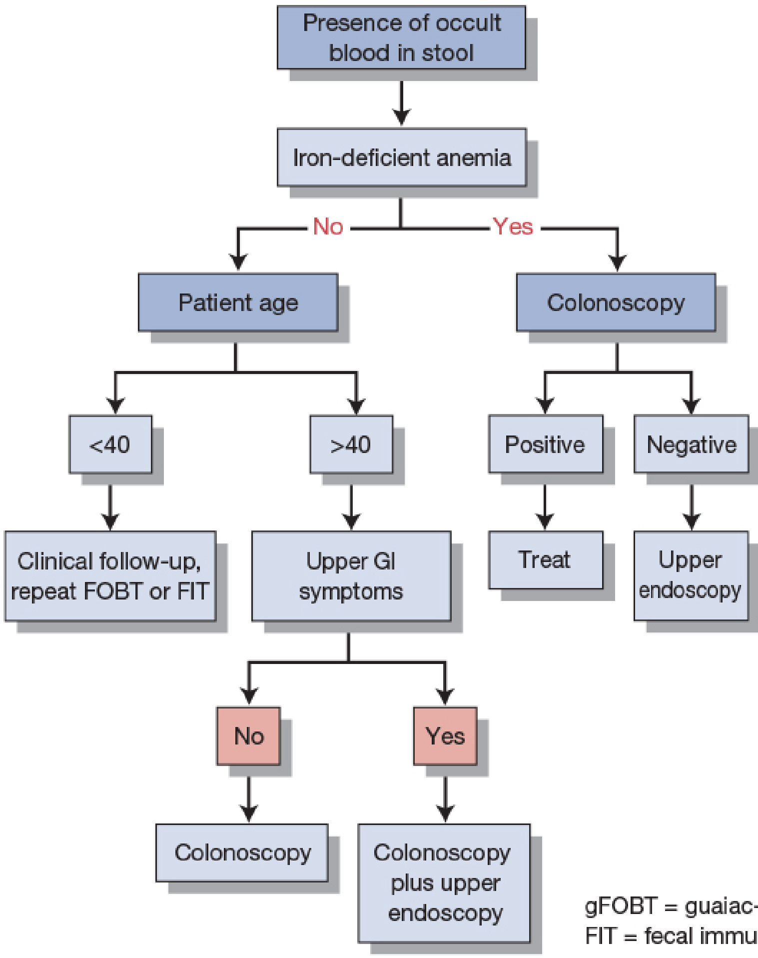
D. Diagnosis

1. Laboratory tests (see also Clinical Pearl 3-6 and Figure 3-8)
   a. Hemoglobin/hematocrit level (may not be decreased in acute bleeds): A hemoglobin level >7 to 8 g/dL is generally acceptable in stable patients without active bleeding. However, patients with acute coronary syndrome should have a higher hemoglobin level >9 to 10 g/dL. If active bleeding or if patient is symptomatic from anemia, transfuse supportively regardless of hemoglobin threshold.
   b. A low mean corpuscular volume (MCV) is suggestive of iron-deficiency anemia (chronic blood loss). Patients with acute bleeding have normocytic or macrocytic red blood cells.
   c. Coagulation profile (platelet count, PT, PTT, INR).
   d. Liver labs, renal function.
   e. The BUN–creatinine ratio is often elevated with upper GI bleeding. This is suggestive of upper GI bleeding if patient has no renal insufficiency. The higher the ratio, the more likely the bleeding is from an upper GI source.
   f. Hemoccult testing (FOBT or FIT) should not be used for inpatient evaluation of GI bleeding (high rates of false positives and false negatives).

CLINICAL PEARL 3-6

Tests to Order in Patients With GI Bleeding

- Hematemesis—Upper endoscopy is the initial test.
- Hematochezia—First rule out an anorectal cause (e.g., hemorrhoids). Colonoscopy should be the initial test because colon cancer is the main concern in patients over age 45.
- Melena—Upper endoscopy is usually the initial test because the most likely bleeding site is in the upper GI tract. Proceed with colonoscopy if no bleeding site is identified from the endoscopy. Push enteroscopy or capsule endoscopy may be used when small bowel bleeding is suspected, or source of bleeding is not identified by upper endoscopy or colonoscopy.
- Occult blood—should only be used in outpatient setting for colorectal cancer screening. A positive test requires colonoscopy.



gFOBT = guaiac-based fecal occult blood test
FIT = fecal immunochemical test

FIGURE 3-8 **Evaluation of occult GI bleeding.**

Quick HIT

If you suspect lower GI bleeding, still exclude upper GI bleeding before attempting to localize the site of the lower GI bleed.

Quick HIT

Initial Steps in any Patient With GI Bleeding

- Vital signs: Hypotension, tachycardia, or orthostatic hypotension are signs of significant hemorrhage. However, vital signs may also be normal when significant hemorrhage is present.
- Obtain intravenous access: two large-bore peripheral IVs or large-bore sheath introducer for unstable patients.
- Resuscitation is the first step (e.g., IV fluids, transfusion).
- Perform rectal examination to look at stool color and presence of blood.

2. Upper endoscopy: most accurate diagnostic test in evaluation of upper GI bleeding. Both diagnostic and potentially therapeutic (coagulate bleeding vessel).
3. Colonoscopy identifies the site of the lower GI bleed in majority of cases, and is both diagnostic and potentially therapeutic.
4. Push enteroscopy can visualize the proximal small bowel when bleeding is suspected there. Video capsule endoscopy is another option for small bowel bleeding when upper and lower endoscopy are unrevealing.
5. Nasogastric tube lavage is no longer routinely used for diagnosis. Historically was used to determine if GI bleed originating from an upper or lower GI source. Studies have not demonstrated benefit in clinical outcomes.
6. Anoscopy can exclude an anal/rectal source.
7. Radionuclide scan (RBC scintigraphy) reveals bleeding even with a low rate of blood loss. It does not localize the lesion; it only identifies active bleeding. It is not used often due to these limitations.
8. CT angiography can be used to localize active bleeding but lacks therapeutic capability.
9. Angiography definitively locates the point of bleeding, but is reserved for patients in whom endoscopy is not an option due to hemodynamic instability.
   a. Should be performed during active bleeding.
   b. Potentially therapeutic (embolization or intraarterial vasopressin infusion).
10. Exploratory laparotomy—rare done, last resort.

CLINICAL PEARL 3-7

Factors That Increase Mortality in GI Bleeding

- Age >65 years
- Severity of initial bleed
- Extensive comorbid illnesses
- Onset or recurrence of bleeding while hospitalized for another condition
- Need for emergency surgery
- Significant transfusion requirements
- Diagnosis (esophageal varices have a 30% mortality rate)
- Endoscopic stigmata of recent hemorrhage

E. Treatment

1. If patient is hemodynamically unstable, resuscitation is always top priority. Remember the ABCs. Once the patient is stabilized, obtain a diagnosis (see also Clinical Pearl 3-7)
   a. Supplemental oxygen
   b. Place two large-bore IV lines. Give IV fluids or blood if patient is volume depleted.
   c. Draw blood for hemoglobin and hematocrit, PT/INR, PTT, and platelet count. Monitor hemoglobin every 4 to 8 hours until the patient is hemoglobin stable for at least 24 hours
   d. Type and cross-match adequate blood (PRBCs). Transfuse as the clinical condition demands (e.g., shock, patients with cardiopulmonary disease)
2. Treatment depends on the cause/source of the bleed
   a. Upper GI bleeding
      - Esophagogastroduodenoscopy (EGD) with coagulation of the bleeding vessel. If bleeding continues, repeat endoscopic therapy or proceed with surgical intervention (ligation of bleeding vessel)
      - If a bleeding ulcer is considered, start a proton pump inhibitor (PPI). Increasing gastric pH improves clotting
      - If suspecting a variceal bleed (e.g., in patients with cirrhosis), start octreotide.

   b. Lower GI bleeding

- Colonoscopy—polyp excision, injection, laser, cautery
- Arteriography with embolization
- Surgical resection of involved area—last resort

3. Indications for angiography or surgery (usually interventional angiography is attempted prior to resorting to surgery):
   a. Hemodynamically unstable patients who have not responded to IV fluid, transfusion, endoscopic intervention, or correction of coagulopathies
   b. Severe initial bleed or recurrence of bleed after endoscopic treatment
   c. Continued bleeding for more than 24 hours
   d. Ongoing transfusion requirement (five units within first 4 to 6 hours)

A 37-year-old man presents with abdominal pain, mild nausea, and dark stools. The patient reports that over the past 6 months he has noticed abdominal pain that is only alleviated by eating. He has gained 6.8 kg (15 lb) during this time period. The patient denies alcohol or illicit drug use, but does report headaches for which he takes over-the-counter acetaminophen. Physical examination reveals melena on rectal examination, but is otherwise unremarkable.

Which of the following is the most likely diagnosis?

A. Peptic ulcer disease
B. Diverticulosis
C. Colon cancer
D. Mesenteric ischemia

- **The answer is A: Peptic ulcer disease.** This patient is presenting with melena (dark tarry stools) and abdominal pain. Peptic ulcer disease is the most common cause of upper GI bleeds, and is suggested by the history. Symptoms from duodenal ulcers are often relieved by eating, and thus are associated with weight gain. **(B)** Diverticulosis is usually asymptomatic; however, if it is associated with GI bleeding, it is typically bright red bleeding. **(C)** Colon cancer should always be considered, but this is a young patient with weight gain, making it less likely. **(D)** Mesenteric ischemia is accompanied by abdominal pain that is worse with eating. However, this patient's abdominal pain improves with eating.

Diseases of the Esophagus

Esophageal Cancer

A. General Characteristics

1. There are two pathologic types. In the past, squamous cell carcinoma (SCC) accounted for majority of cases. However, the incidence of adenocarcinoma has increased dramatically in the United States, and it now accounts for >60% of new cases. Worldwide, SCC is still most common.
   a. SCC
      - Incidence is higher in Black Americans and men compared to other groups.
      - Most common locations are the upper and midthoracic esophagus. About one-third may be in distal 10 cm of esophagus.
      - Risk factors are **alcohol and tobacco use**, diet (nitrosamines, betel nuts, chronic ingestion of hot foods and beverages such as tea), human papillomavirus, achalasia, Plummer–Vinson syndrome, caustic ingestion, and nasopharyngeal carcinoma.

   b. Adenocarcinoma
      - Incidence is higher in White Americans and men.
      - Most common in distal third of the esophagus/gastroesophageal junction (in 80% of cases).
      - Risk factors: **GERD and Barrett esophagus** are main risk factors; alcohol and tobacco may not be as important as in SCC.
2. **The prognosis is poor:** Five-year survival rate is about 30% to 45% if locoregional disease, but only 5% if distant metastasis present at diagnosis.
3. Staging
   a. Stage I—tumor invades lamina propria or submucosa; nodes negative
   b. Stage IIa—tumor invades muscularis propria or adventitia; nodes negative
   c. Stage IIb—tumor invades up to muscularis propria; positive regional nodes

d. Stage III—tumor invades adventitia (positive regional nodes) **or** tumor invades adjacent structures (positive or negative nodes)
e. Stage IV—distant metastasis

Quick HIT

Barrett esophagus is a complication of long-standing acid reflux disease in which there is columnar metaplasia of the squamous epithelium. Patients with Barrett esophagus are at increased risk of developing adenocarcinoma of the esophagus. Monitor these patients with routine endoscopic surveillance.

B. Clinical Features

- Dysphagia—most common symptom (initially solids only, then progression to liquids)
- Weight loss—second most common symptom
- Anorexia
- Odynophagia (pain with swallowing)
- Ironic deficiency anemia (usually chronic occult GI blood loss)
- Cough or hoarseness of voice (recurrent laryngeal nerve involvement)
- Aspiration pneumonia
- Tracheoesophageal or bronchoesophageal fistula (late complication)
- Chest pain

C. Diagnosis

1. Upper endoscopy with biopsy is required for definitive diagnosis. It confirms the diagnosis in majority of cases.
2. Endoscopic ultrasound helps determine the depth of penetration of the tumor and is the most reliable test for staging local cancer.
3. Full metastatic workup (e.g., CT scan of the neck/chest/abdomen, PET/CT).

D. Treatment

1. Palliation is the goal in most patients because the disease is usually advanced at presentation.

2. Surgery (esophagectomy) may be curative for patients with local disease (no nodal or distant metastases).
3. Chemotherapy, immunotherapy, and radiation in addition to surgery may prolong disease-free survival more than surgery alone.

Achalasia

A. General Characteristics

1. Acquired motor disorder of esophageal smooth muscle in which the lower esophageal sphincter (LES) fails to completely relax with swallowing, and abnormal peristalsis of esophageal body replaces normal peristalsis
2. Absolute criteria for diagnosis
   a. Incomplete relaxation of the LES
   b. Aperistalsis of esophagus

B. Causes

1. The majority in the United States are idiopathic.
2. In the United States, adenocarcinoma of proximal stomach is the second most common cause.
3. Worldwide, Chagas disease is an important cause.

C. Clinical Features

1. Dysphagia (odynophagia is less common)
   a. Equal difficulty swallowing solids and liquids (in contrast to mechanical obstruction such as esophageal cancer, in which dysphagia for solids starts first, then later for liquids).
   b. Patients tend to eat slowly and drink lots of water to wash down food. Also, they may twist their body, extend their neck, or walk about the room in an effort to force food into the stomach
   c. It is exacerbated by fast eating and emotional stress
2. Regurgitation
   a. Food gets “stuck” in the esophagus and then comes back up.
   b. Regurgitation may lead to aspiration
3. Chest pain or burning discomfort

4. Weight loss
5. Recurrent pulmonary complications secondary to aspiration, which may cause lung abscess, bronchiectasis, or hemoptysis

Quick HIT

Patients with achalasia have a sevenfold increase in the risk of esophageal cancer (usually squamous cell)—it occurs in 10% of patients 15 to 25 years after the initial achalasia diagnosis. Often tumors go unnoticed (even when large) due to a dilated esophagus and chronic dysphagia. Therefore, perform surveillance esophagoscopy to detect the tumor at an early stage.

D. Diagnosis

1. Barium esophagram (Figure 3-9)—typical finding is "bird's beak" appearance—beak-like narrowing of distal esophagus and a large, dilated esophagus proximal to the narrowing. Not a sensitive test for achalasia, as high rate of falsely normal results.
2. Upper GI endoscopy—to rule out secondary causes of achalasia (gastric carcinoma) and retention esophagitis or esophageal cancer.
3. Esophageal manometry—required to confirm the diagnosis; reveals failure of LES relaxation and aperistalsis of esophageal body.

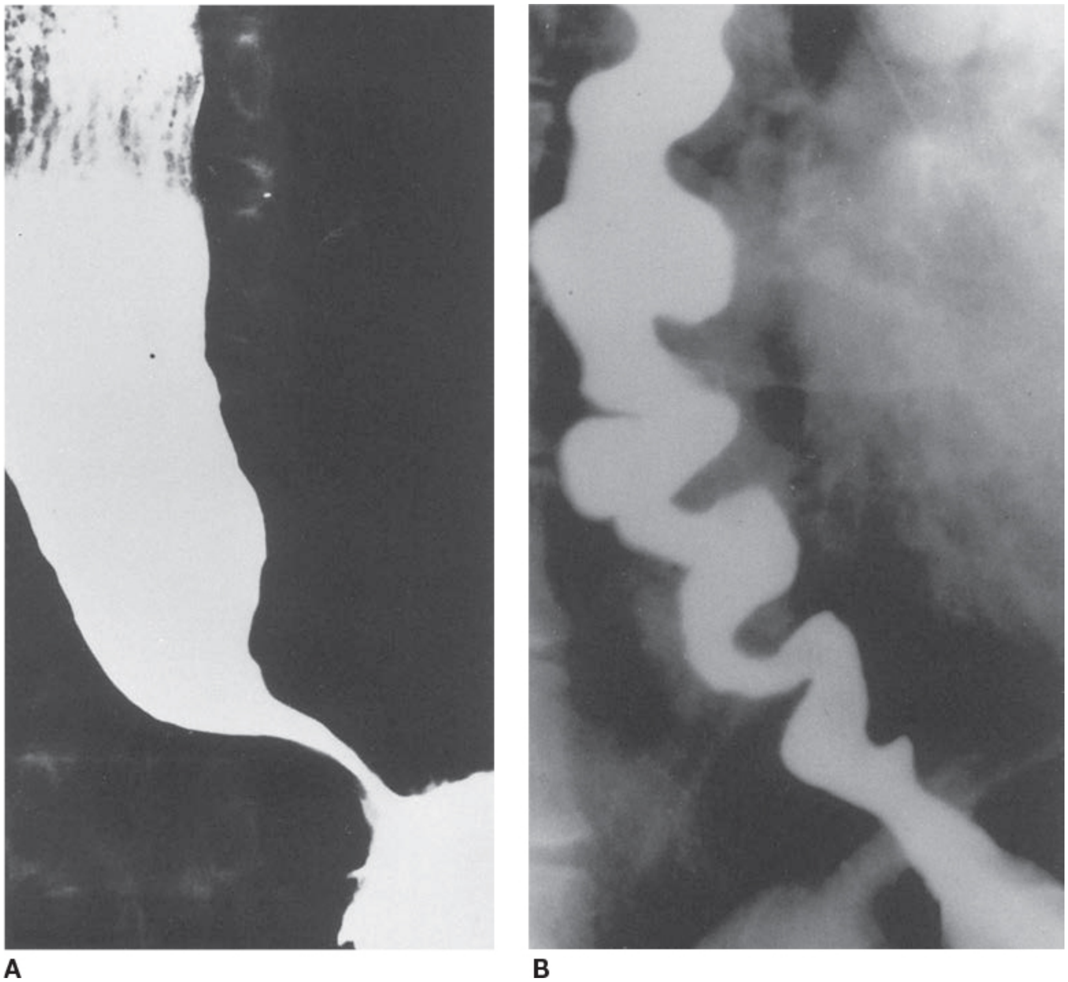


FIGURE 3-9 Radiographs of achalasia (A) and diffuse esophageal spasm (B).
(Reprinted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:821. Figure 106.4.)

E. Treatment

1. Instruct patient on adaptive measures: chew food to consistency of pea soup before swallowing; sleep with trunk elevated; avoid eating before sleep
2. Medical therapy
   a. Sublingual nitroglycerin and nitrates to relax smooth muscle of LES
      - May improve swallowing in early stages of achalasia (before esophageal dilatation occurs)

- Most useful in the short-term treatment of achalasia (before more definitive therapy)

3. Injection of botulinum toxin into the LES during endoscopy
   a. Blocks cholinergic activity in the LES
   b. Can be effective but often require repeat procedures within 1 to 2 years
4. Pneumatic dilatation
   a. Lowers basal LES tone by disrupting the muscular ring
   b. Can be effective, but there is a 5% risk of perforation
5. Surgical
   a. “Heller myotomy”—circular muscle layer of LES is incised
   b. Usually reserved for patients who do not respond to dilation therapy
6. Although most interventions have high success rates of relieving dysphagia, many will require repeat treatment within 10 years

Quick HIT

There is no cure for Achalasia. Treatment modalities (including surgery) are only palliative.

Quick HIT

It can be difficult to distinguish the chest pain of diffuse esophageal spasm (DES) from cardiac chest pain. Therefore, many patients undergo a cardiac workup, including cardiac catheterization, to rule out ischemic causes of chest pain, before an esophageal cause is investigated.

Diffuse Esophageal Spasm

A. General Characteristics

1. Nonperistaltic spontaneous contraction of the esophageal body—several segments of the esophagus contract simultaneously and prevent appropriate advancement of food bolus.
2. In contrast to achalasia, **sphincter function is normal** (normal LES pressure).

B. Clinical Features

1. **Chest pain** that mimics cardiac angina and may radiate to the jaw, arms, and back.
2. Dysphagia with both solids and liquids is common; however, regurgitation of food is uncommon.

C. Diagnosis

1. Esophageal manometry is diagnostic—simultaneous, multiphasic, repetitive contractions that occur after a swallow; sphincter response is normal.
2. Upper GI endoscopy to rule out other esophageal disorders such as esophageal cancer.
3. Upper GI barium esophagram ("**corkscrew esophagus,**" which represents multiple simultaneous contractions). However, barium esophagram is neither sensitive nor specific for diagnosis of DES.

D. Treatment

1. In general, there is no completely effective therapy—treatment failure rates are high.
2. Medical treatment involves nitrates and calcium channel blockers (decreases amplitude of contractions). PPI for GERD symptoms. Tricyclic antidepressants may provide symptomatic relief.
3. Endoscopic botulinum toxin injection may be an option for those in whom medical therapy is not effective.

Esophageal Hiatal Hernias

A. General Characteristics

There are two types of hiatal hernias: sliding (type 1) and paraesophageal (type 2) (Figure 3-10).

1. Sliding hiatal hernias (type 1) account for >95% of cases. Both the gastroesophageal junction and a portion of the stomach herniate into the thorax through the esophageal hiatus (so that the gastroesophageal junction is above the diaphragm). This is a common and benign finding that is associated with GERD.

2. Paraesophageal hiatal hernia (types 2 to 4) accounts for <5% of cases. In type 2 hernias, the stomach herniates into the thorax through the esophageal hiatus, but the gastroesophageal junction does not; it remains below the diaphragm. Type 3 hernias have elements of type 1 and type 2 hernias, and both the fundus and the GE junction herniate through the hiatus. Type 4 hernias include organs other than the stomach in the hernia sac.

Quick HIT

- Paraesophageal hernias tend to enlarge with time, and the entire stomach may ultimately move into the thorax.
- Type 3 hernias (combination of type 1 and 2) are treated as type 2 hernias (surgically).

B. Clinical Features

1. The majority of cases are asymptomatic and discovered incidentally.
2. Possible symptoms include heartburn, chest pain, and dysphagia.
3. Complications of sliding hiatal hernias include GERD (most common), reflux esophagitis (with risk of Barrett esophagus/cancer), and aspiration.
4. Complications of paraesophageal hernias are potentially life threatening and include obstruction, hemorrhage, incarceration, and strangulation.

Quick HIT

If a patient with GERD also has a hiatal hernia, the hernia often worsens the symptoms of GERD.

C. Diagnosis—barium esophagram and upper endoscopy

D. Treatment

- Type 1 hernias are treated medically (with antacids, small meals, and elevation of the head after meals); a small percentage of cases may

require surgery (Nissen fundoplication), if there is no response to medical therapy or if there is evidence of esophagitis.
- Type 2 to 4 hernias are treated with elective surgery if symptomatic or a complication occurs. Elective repair for asymptomatic patients is controversial.

Mallory–Weiss Syndrome

- This is a mucosal tear in the distal esophagus or proximal stomach as a result of forceful vomiting or retching. It usually occurs after repeated episodes of vomiting, but it may also occur after just one episode.
- It is most commonly associated with heavy alcohol use leading to vomiting, but any disorder that causes vomiting can induce the mucosal tear.
- Hematemesis or coffee-ground emesis is usually present—may be accompanied by epigastric pain.
- Upper endoscopy is diagnostic.
- Most cases (90%) stop bleeding with supportive care.
- Treatment consists of acid suppression (PPI), antiemetics to prevent vomiting, and endoscopic therapy if actively bleeding. If bleeding persists or recurs, angiography with transarterial embolization is an option.

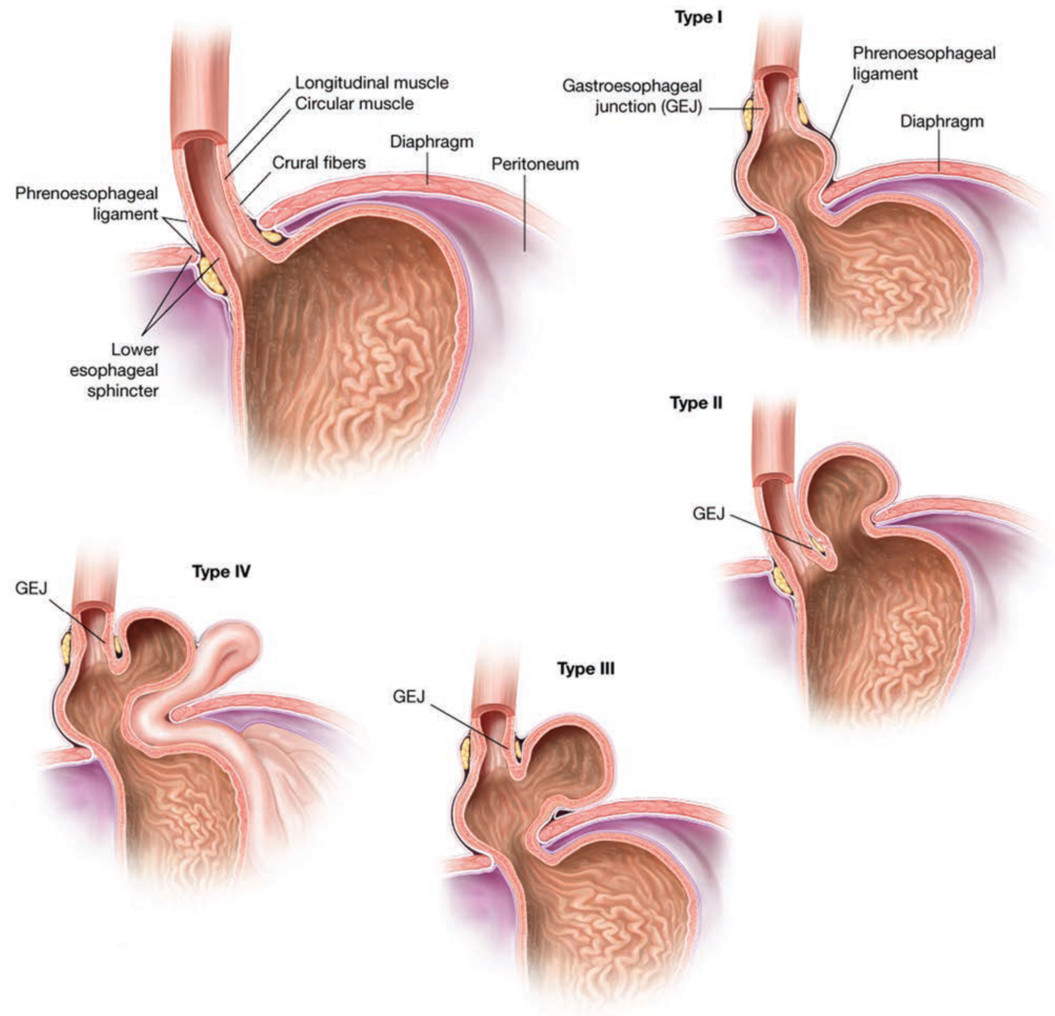


FIGURE 3-10 **Types of esophageal hiatal hernias.**
(Reprinted with permission from Mulholland MW, Albo D, Dalman RL, et al. *Operative Techniques in Surgery*. Wolters Kluwer; 2014.)

Quick HIT

During forceful vomiting, the marked increase in intraabdominal pressure is transmitted to the esophagus. This can lead to two conditions, depending on the severity and location of the tear.

- If the tear is mucosal and at the distal esophagus or proximal stomach, it is referred to as **Mallory–Weiss syndrome.**
- If a tear is transmural (causing esophageal perforation), it is referred to as **Boerhaave syndrome.**

Plummer–Vinson Syndrome (Upper Esophageal Webs)

- Rare disorder with triad of dysphagia, iron-deficiency anemia, and cervical esophageal web. Other findings include *koilonychia* (spoon-shaped fingernails) and atrophic oral mucosa.
- Ten percent of patients develop SCC of the oral cavity, hypopharynx, or esophagus; therefore, this is considered a premalignant lesion.
- Treatment: esophageal dilatation; correct iron deficiency.

Esophageal Rings (Schatzki Ring)

- Schatzki ring is a type of circumferential ring usually in the distal esophagus that is almost always accompanied by a hiatal hernia
- It is usually asymptomatic, but mild to moderate dysphagia to solids may be present
- Most common cause is thought to be long-standing GERD. Can also form after ingestion of alkali, acids, bleach, or detergents (e.g., in suicide attempts). Ingesting alkali is more dangerous to esophagus than acid because it may lead to liquefactive necrosis of the esophagus with full-thickness perforation
- Complications: stricture formation
- Treatment is endoscopic dilation and antacid therapy (PPI)

Esophageal Diverticula

- Most esophageal diverticula are caused by an **underlying motility disorder** of the esophagus (Figure 3-11).
- **Zenker diverticulum** is the most common type; found in upper third of the esophagus.
- Failure of the cricopharyngeal muscle to relax during swallowing leads to increased intraluminal pressure. This causes outpouching of mucosa through an area of weakness in the pharyngeal constrictors.
- Clinical features include dysphagia, regurgitation, halitosis (bad breath), weight loss, and chronic cough.
- It is typically seen in patients >50 years old.

- **Traction diverticula** are located in the midpoint of the esophagus, due to traction from contiguous mediastinal inflammation and adenopathy. Pulmonary tuberculosis is a common cause. It is usually asymptomatic and does not require treatment.
- **Epiphrenic diverticula** are found in lower third of esophagus and are usually associated with esophageal dysmotility. Symptoms of dysphagia are more often related to the underlying motility disorder, unless the diverticulum is very large.
- Barium swallow is the best diagnostic test for diverticula.
- Treatment of symptomatic Zenker diverticula is surgery. Cricopharyngeal myotomy has excellent results. Treatment of symptomatic epiphrenic diverticula is targeted toward underlying motility disorder. Diverticulectomy, myotomy, or fundoplication may be needed.

***Quick* HIT**

An underlying motility disorder is the cause of both proximal **(Zenker)** and distal **(epiphrenic) esophageal diverticula.** Surgical treatment is aimed at correcting the motility disorder (i.e., myotomy). Diverticulectomy is of secondary importance.

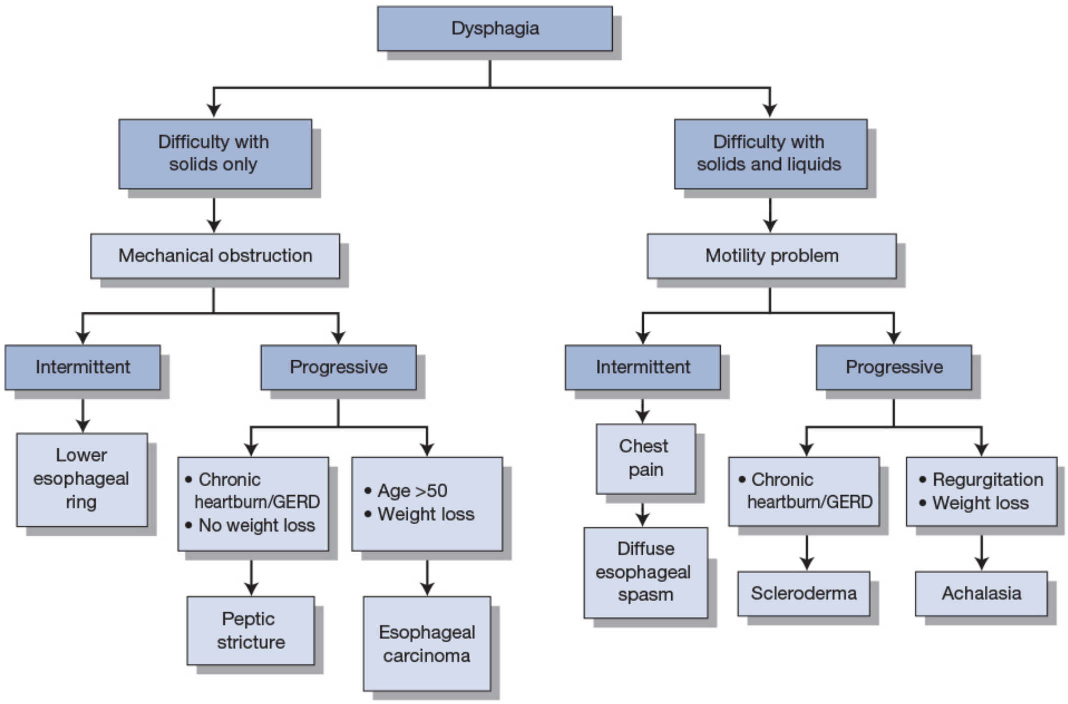


FIGURE 3-11 **Causes of dysphagia.**

Quick HIT

If gastric/esophageal contents leak into the mediastinum or pleura, infection and sepsis may result.

Esophageal Perforation

- Etiology: blunt trauma, penetrating trauma, iatrogenic injury (endoscopy, cardiac ablation, etc.), forceful vomiting **(Boerhaave syndrome)**.
- Clinical features: pain (severe retrosternal chest, neck, epigastric or shoulder pain), odynophagia, dyspnea, signs of sepsis (fever, tachypnea, tachycardia, hypotension), *Hamman sign* ("mediastinal crunch" produced by the heart beating against air-filled tissues), pneumothorax, or pleural effusion.
- Contrast esophagram is definitive diagnostic study (soluble Gastrografin swallow preferred).
- CXR usually shows air in the mediastinum.

- CT of chest and abdomen if unable to obtain contrast esophagram and to look for fluid collections requiring drainage
- If the patient is stable and the perforation is small (draining into lumen), medical management is appropriate: IV fluids, NPO, antibiotics, and PPI.
- If patient is ill and the perforation is large (or if there is communication into pleural cavity), surgery should be performed within 24 hours of presentation (success rate is higher)

Quick HIT

The time interval between esophageal perforation and surgery is the most important factor in determining survival. **If surgery is delayed beyond 24 hours, the mortality rate and the likelihood of complications increase.**

Quick HIT

Most cases of PUD are due to *H. pylori* infection and NSAID use. It can be difficult to determine the cause in a patient with *H. pylori* infection who also uses NSAIDs. Both may be responsible. Therefore, if in doubt, test for *H. pylori.*

Diseases of the Stomach

Peptic Ulcer Disease

A. Causes

1. Most common causes
   a. NSAIDs—inhibit prostaglandin production, which leads to impaired mucosal defenses
   b. *H. pylori* infection
   c. Acid hypersecretory states, such as Zollinger–Ellison syndrome
2. Other risk factors associated with higher risk of PUD (have not been shown to be causative)

a. Smoking
b. Alcohol use
c. Genetic predisposition
d. Psychological stress and dietary factors (such as coffee and spice intake) have not been shown to be associated with higher risk of PUD

B. Clinical Features

1. Epigastric pain
   a. Aching or gnawing in nature
   b. **Nocturnal symptoms and the effect of food on symptoms are variable** (see Table 3-5)
2. May be complicated by upper GI bleeding, gastric outlet obstruction, fistulization, and perforation
3. Other symptoms: nausea/vomiting, bloating, early satiety, and weight loss
4. Many are asymptomatic

Quick HIT

Gastric ulcers have a higher risk of malignancy than duodenal ulcers. If the ulcer has suspicious features on endoscopy (ulcerated mass, irregular folds or margins), biopsy is indicated.

C. Diagnosis

1. Endoscopy
   a. Most accurate test in diagnosing ulcers.
   b. Essential in diagnosis of gastric ulcers because biopsy is necessary to rule out malignancy.
   c. Preferred when severe or acute bleeding is present (can perform electrocautery of bleeding ulcers).
   d. Can obtain endoscopic biopsy for diagnosis of *H. pylori.*
2. Laboratory test—for diagnosis of *H. pylori* infection
   a. Biopsy: Histologic evaluation of endoscopic biopsy is the gold standard.

b. Stool antigen test—High sensitivity and ease of testing makes this ideal for screening. Results can be affected by bismuth, antibiotics, and PPIs (need to be off these medications for several weeks before testing).
c. Urease detection via urea breath test is highly sensitive and specific. It documents active infection and helps to assess the results of antibiotic therapy. Also must be off bismuth, antibiotics, and PPIs.
d. Serology (lower specificity)—The presence of antibodies to *H. pylori* does not distinguish between active and prior infection—antibodies to *H. pylori* can remain elevated for months or even years after eradication of infection.

3. Serum gastrin measurement—if considering Zollinger–Ellison syndrome as a diagnosis.

TABLE 3-5 Duodenal Versus Gastric Ulcers

	Duodenal Ulcers	Gastric Ulcers
Pathogenesis	Caused by an increase in offensive factors (higher rates of basal and stimulated gastric acid secretion)	Caused by a decrease in defensive factors (gastric acid level is normal/low unless ulcer is pyloric or prepyloric)
Malignant potential	Low	High (5–10% are malignant)—should undergo biopsy to rule out malignancy
Location	Majority are 1–2 cm distal to pylorus and on posterior wall	Type I (most common, 70%): on lesser curvature
		Type II: gastric and duodenal ulcer
		Type III: prepyloric (within 2 cm of pylorus)
		Type IV: near esophagogastric junction
Age distribution	Tends to occur in younger patients (age <50)	Tends to occur in older patients (age > 60 years)
Risk factors	NSAIDs, *H. pylori* infection, smoking, alcohol	NSAIDs, *H. pylori* infection, smoking, alcohol
Other	**Pain occurs several hours after eating**	**Eating worsens pain**
	Nocturnal pain is more common than in gastric ulcers	Complication rates are higher than those of duodenal ulcers. There is a higher recurrence rate with medical therapy alone

D. Treatment

1. Medical—Majority of patients with PUD can be successfully treated by curing *H. pylori* infection, avoidance of NSAIDs, and appropriate use of antisecretory drugs.
   a. Supportive (lifestyle modifications)
      - Discontinue NSAIDs
      - Restrict alcohol use. Dietary restrictions are not supported by evidence.
      - Smoking cessation

- Avoid eating before bedtime (eating stimulates nocturnal gastric acid levels).

b. Antisecretory therapy

- PPIs—for example, pantoprazole, omeprazole, block H^+/K^+ ATPase pump directly in parietal cell membrane. First line of therapy, most effective antisecretory agents.
- H_2-Receptor blockers— for example, famotidine, ranitidine. Block histamine-based parietal cell acid secretion. Less effective than PPIs
- Antacids—not recommended for primary therapy. More appropriately used for adjunct therapy/symptomatic relief. Examples include aluminum hydroxide, calcium carbonate, bismuth subsalicylate
- Duration of PPI is usually for 4 to 8 weeks. Some patients may benefit from maintenance PPI

c. Eradicate *H. pylori* with triple or quadruple therapy (see Table 3-6). Once infection is cleared, the rate of recurrence is very low

- For initial therapy, triple therapy (PPI, amoxicillin, and clarithromycin) for 14 days
- Quadruple therapy (PPI, bismuth, metronidazole, and tetracycline) indicated for patients with risk factors for macrolide resistance

2. Surgical

a. Rarely needed electively

b. Required for the complications of PUD (bleeding, perforation, gastric outlet obstruction, suspected malignancy) (see Table 3-7 and Figure 3-12)

Quick HIT

Acid Suppression Therapy (PPIs)

- Omeprazole
- Pantoprazole
- Esomeprazole
- Dexlansoprazole
- Lansoprazole
- Rabeprazole

TABLE 3-6 *Helicobacter pylori* Eradication

	Regimen	Advantage	Disadvantage
Triple therapy	PPI plus amoxicillin and clarithromycin	Twice-daily dosing	More expensive than bismuth-based triple therapy
Quadruple therapy	PPI, bismuth subsalicylate, metronidazole, and tetracycline	Useful in patients with risk for macrolide resistance	May require four times daily dosing Expense of PPI

Acute Gastritis

- Acute gastritis refers to inflammation of the gastric mucosa.
- There are multiple causes: NSAIDs; *H. pylori* infection; alcohol, heavy cigarette smoking, cocaine; extreme physiologic stress (e.g., trauma, shock, sepsis, burns).
- It can either be asymptomatic or cause epigastric pain.
- If epigastric pain is low or moderate and is not associated with worrisome symptoms/findings, empiric therapy with acid suppression is appropriate. Stop NSAIDs.
- If there is no positive response after 4 to 8 weeks of treatment, consider a diagnostic workup. Include upper GI endoscopy and ultrasound (to rule out gallstones), and test for *H. pylori* infection.
- If *H. pylori* infection is confirmed, antibiotic therapy is indicated (see Table 3-6).

Quick HIT

Upper GI endoscopy is the best test for evaluating a patient with epigastric pain. It can diagnose PUD, gastritis, and esophagitis. It can also rule out cancers of the esophagus and stomach, and *H. pylori* infection with biopsy.

Chronic Gastritis

- The most common cause is *H. pylori* infection (over 80% of cases).

- Autoimmune gastritis leads to chronic atrophic gastritis with serum antiparietal and antiintrinsic factor antibodies (and possible development of pernicious anemia).
- Most patients with chronic gastritis due to *H. pylori* are asymptomatic and never develop complications. The condition may manifest as epigastric pain similar to PUD.
- Complications include PUD, gastric cancer, and mucosa-associated lymphoid tissue lymphoma.
- Upper GI endoscopy with biopsy is the test of choice for diagnosis of chronic gastritis. Other tests should be used to find the cause (usually *H. pylori*).
- If the patient is symptomatic, treatment involves *H. pylori* eradication with triple or quadruple therapy (see Table 3-6).

TABLE 3-7 Complications of Peptic Ulcer Disease

	Clinical Findings	Diagnostic Studies	Management	Other
Perforation Or Penetration	Acute, severe abdominal pain, signs of peritonitis, hemodynamic instability	CT scan is the most sensitive test (detects free abdominal air and can localize site of penetration)	Emergency surgery to close perforation and perform definitive ulcer operation	**Can progress to sepsis and death if untreated**
Gastric Outlet Obstruction	Nausea/vomiting (poorly digested food), epigastric fullness/early satiety, weight loss	Barium swallow, CT, and upper endoscopy	Initially, nasogastric suction; correct electrolyte/volume deficits; supplement nutrition. Endoscopic dilation or surgery is eventually necessary in some patients.	Most common with duodenal ulcers and type III gastric ulcers
GI Bleeding	Bleeding may be slow (leading to iron-deficiency anemia) or can be rapid and severe (leading to shock)	Upper GI endoscopy (diagnostic and therapeutic)	Resuscitation; diagnose site of bleed via endoscopy and treat; perform surgery or embolization for acute bleeds that require transfusion of ≥6 units of blood	**Peptic ulcer disease is the most common cause of upper GI bleeding**

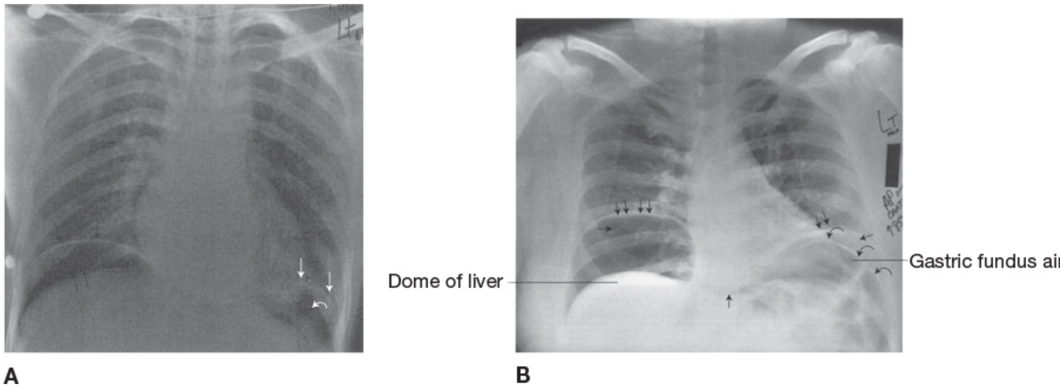


FIGURE 3-12 **A: An AP chest radiograph in a patient with a perforated duodenal ulcer and acute abdomen. The *curved arrow* shows free subdiaphragmatic air due to the perforated ulcer. The *straight arrows* show the diaphragms bilaterally. B: Chest radiograph (upright) showing bilateral subdiaphragmatic intraperitoneal air. *Double arrows* represent right and left hemidiaphragms. Note the bilateral subdiaphragmatic air (*straight and curved arrows*). There is air in the gastric fundus as well as free air surrounding the gastric fundus.**
(Reprinted with permission from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Lippincott-Raven; 1998:103, Figure 6-46, and 159, Figure 8-22, respectively.)

***Quick* HIT**

Metastases of Gastric Carcinoma—Common Eponyms

- **Krukenberg tumor**—metastasis to the ovary
- **Blumer shelf**—metastasis to the rectum (pelvic cul-de-sac)—can palpate on rectal examination
- **Sister Mary Joseph node**—metastasis to the periumbilical lymph node
- **Virchow node**—metastasis to the supraclavicular fossa nodes
- **Irish node**—metastasis to the left axillary adenopathy

Gastric Cancer

A. General Characteristics

1. The majority are adenocarcinomas
2. Gastric cancer is rare in the United States (more common in Eastern Asia, Eastern Europe, and South America, and resource-limited

countries)

3. Morphology
   a. Ulcerative carcinoma—ulcer through all layers
   b. Polypoid carcinoma—solid mass projects into stomach lumen
   c. Superficial spreading—most favorable prognosis
   d. *Linitis plastica*—“leather bottle”—infiltrates early through all layers, stomach wall is thick and rigid, poor prognosis

B. Risk Factors

1. Intestinal metaplasia, gastric dysplasia
2. Gastric polyps, chronic atrophic gastritis
3. *H. pylori* infection—sixfold increase in risk
4. Family history and genetic polymorphisms
5. Postantrectomy—after Billroth II anastomosis (15 to 20 years after surgery)
6. Pernicious anemia—threefold increase in risk
7. Hypertrophic gastropathy (Ménétrier disease)
8. High intake of preserved foods (high salt, nitrates, nitrites—smoked fish)
9. Smoking
10. Blood type A

C. Clinical Features

1. Abdominal pain and unexplained weight loss are most common symptoms.
2. Reduced appetite, anorexia, dyspepsia, early satiety
3. Nausea and vomiting, dysphagia, occult GI bleeding, iron-deficiency anemia, melena

D. Diagnosis

1. Upper endoscopy with multiple biopsies—most accurate test and provides tissue diagnosis
2. Barium upper GI series—less accurate, but can complement upper endoscopy/biopsy findings
3. CT scan of chest, abdomen, and pelvis with contrast—for staging and to detect the presence of metastases

E. Treatment

1. Surgical resection with wide (>5 cm) margins (total or subtotal gastrectomy) with extended lymph node dissection. Endoscopic resection may be appropriate for small tumors with low risk for nodal metastases.
2. Chemotherapy or radiation may be appropriate in some cases (especially in unresectable disease).

Gastric Lymphoma

- A rare type of non-Hodgkin lymphoma that arises in the stomach.
- Clinical features are nonspecific and similar to those of adenocarcinoma of the stomach (e.g., abdominal pain, weight loss, anorexia).
- Complications include bleeding, obstruction, and perforation (possibly presented as an emergency).
- EGD with biopsy is the standard for diagnosis.
- Treatment depends on the stage of the disease and the presence of complications. Options include surgical resection, radiation, and chemotherapy.

Diseases of the Small Intestine

Small Bowel Obstruction

A. General Characteristics

1. There are three main points of differentiation to consider in small bowel obstruction (SBO).
   a. Partial versus complete obstruction
      - With partial obstruction, patients are able to pass gas or have bowel movements, as opposed to complete obstruction
      - However, patients with complete obstruction may occasionally be able to pass gas or stool because they may have residual stool or gas in the colon

   b. Closed-loop versus open-loop obstruction

- With closed-loop obstruction, the lumen is occluded at two points by an adhesive band or hernia ring. This can compromise the blood supply, requiring emergent surgery

c. Proximal versus distal SBO
- Distal obstruction causes distention of proximal bowel segments, making diagnosis easier on plain radiograph

2. Pathophysiology

a. **Dehydration is a key event in SBO.** Intestinal distention causes reflex vomiting, increased intestinal secretion proximal to the point of obstruction, and decreased absorption. This leads to hypochloremia, hypokalemia, and metabolic alkalosis

b. The resulting hypovolemia leads to systemic findings such as tachycardia, hypotension, tachypnea, altered mental status, and oliguria

***Quick* HIT**

SBO

- Proximal obstruction: frequent vomiting, severe pain, minimal abdominal distention
- Distal obstruction: less frequent vomiting and significant abdominal distention

***Quick* HIT**

Excessively high intraluminal pressure may compromise blood supply, leading to strangulation. This can lead to shock, gangrene, peritonitis, or perforation of bowel—all devastating complications.

Quick HIT

Large Bowel Obstruction

- Causes: colon cancer (most common cause), volvulus, adhesions, hernias, strictures
- Results in less fluid and electrolyte disorders than SBO
- See Figure 3-13 for radiographic findings

B. Causes

1. Adhesions from previous abdominal surgery—most common cause in adults.
2. Incarcerated hernias—second most common cause.
3. Malignancy (including peritoneal carcinomatosis), intussusception, Crohn disease, and superior mesenteric artery syndrome (compression of third portion of duodenum).

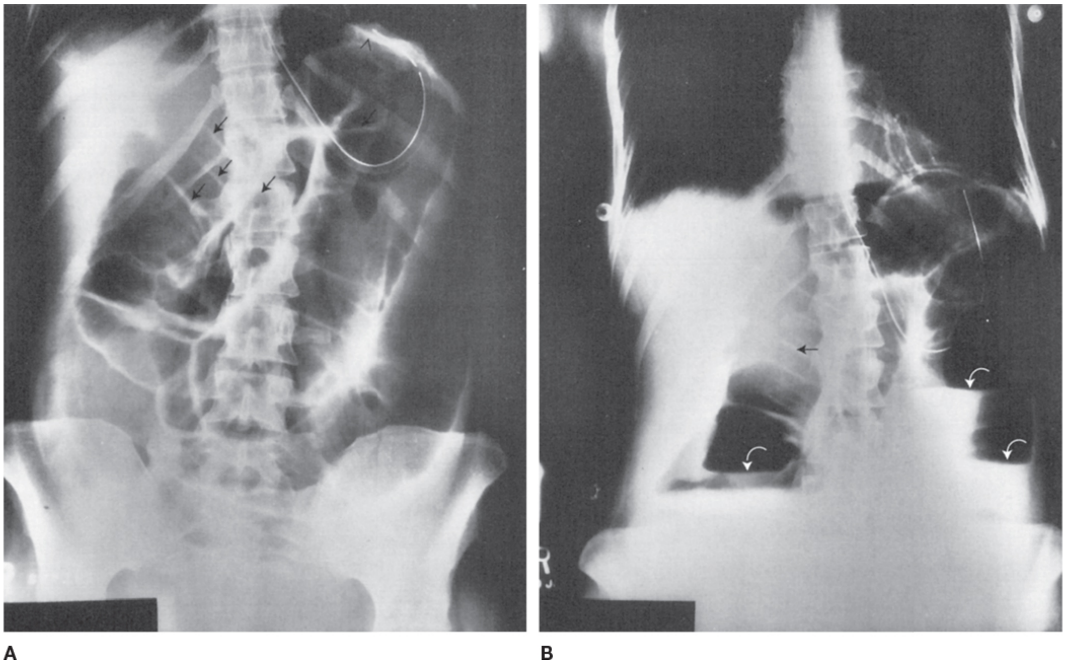


FIGURE 3-13 **A: An AP supine film of large bowel obstruction. Note the dilated air-filled proximal colon with an absence of air in the distal colon. B: An AP upright film of large bowel obstruction. Note multiple colon air–fluid levels (*curved arrow*).**

(Reprinted with permission from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Lippincott-Raven; 1998:158. Figure 8-21A and B.)

C. Clinical Features

1. Acute onset cramping abdominal pain—if pain is continuous and severe, strangulation or peritonitis from perforation may be present
2. Nausea, vomiting—may be feculent
3. Obstipation (absence of stool and flatus)
4. Abdominal distention
5. Signs of hypovolemia (tachycardia, orthostatic hypotension)

D. Diagnosis

1. Abdominal plain films (upright or lateral decubitus and supine films) —dilated loops of small bowel, air–fluid levels proximal to point of obstruction (on upright film), and minimal gas in colon (if complete SBO) (Figure 3-14).

2. CT abdomen and pelvis—to evaluate severity, location, and potential complications of obstruction. IV and PO contrast are ideal (omit PO contrast if suspect complete obstruction).

Quick HIT

Manifestations of bowel compromise in SBO include fever, severe and continuous pain, peritoneal signs, SIRS, gas in the bowel wall or portal vein, abdominal free air, and metabolic acidosis.

E. Treatment

1. Nonoperative management—appropriate if bowel obstruction is incomplete and there is no fever, tachycardia, peritoneal signs, or leukocytosis. Surgical consultation is always indicated.
   a. Bowel rest (NPO)
   b. IV fluids to establish adequate urine output; replete electrolyte abnormalities (usually require potassium repletion)
   c. Nasogastric tube to empty stomach (gastric decompression)
2. Surgery is indicated for complete obstruction, closed-loop obstruction, failure of nonoperative management, or if bowel compromise (ischemia, necrosis, or perforation) is suspected. Perform an exploratory laparotomy **with lysis of adhesions and resection of any necrotic bowel**

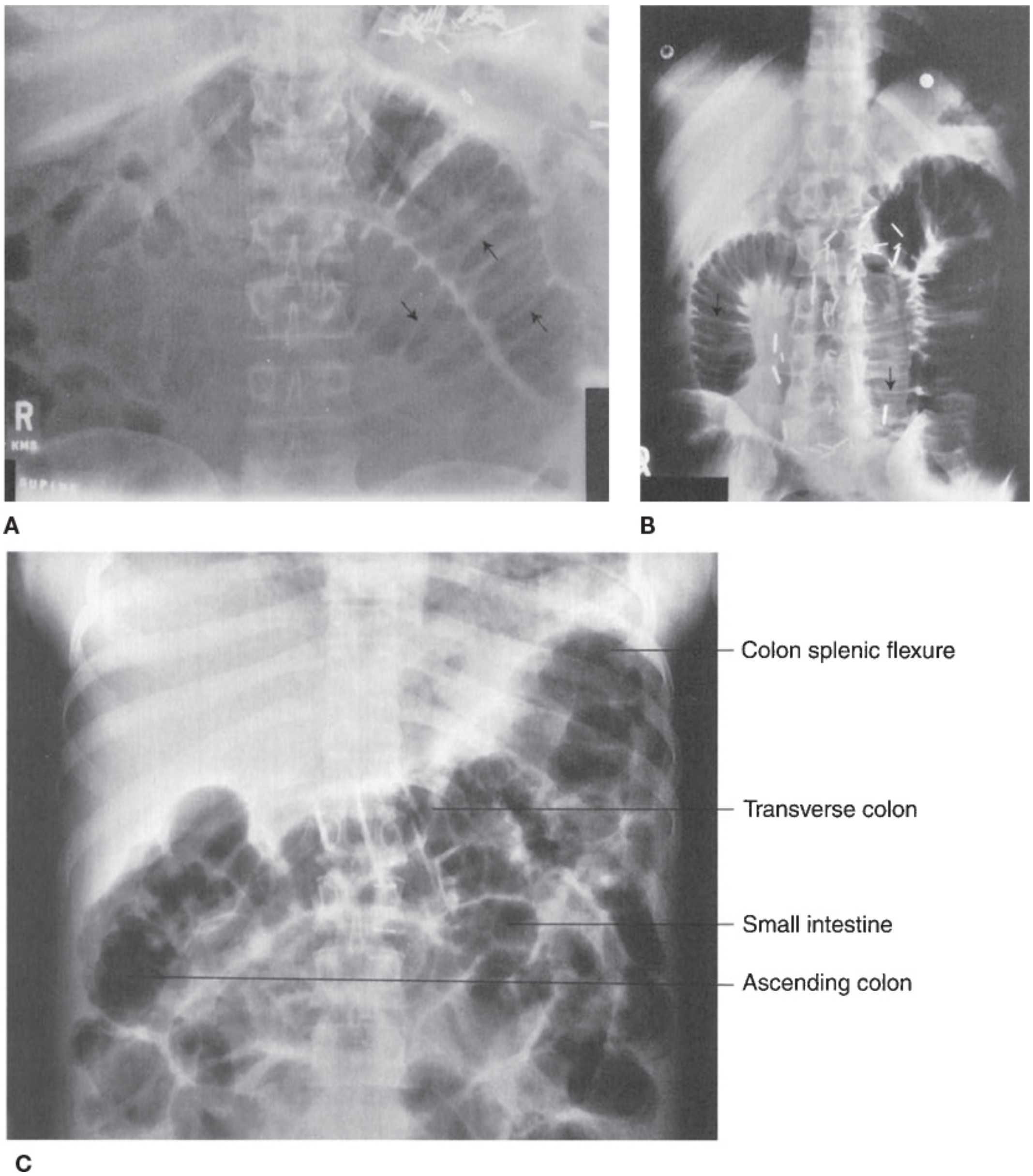


FIGURE 3-14 A: An AP supine film of small bowel obstruction shows prominent valvulae conniventes (*arrows*). Air is confined to the small bowel, with no obvious air in the colon. Note surgical clips from previous surgery. B: An AP upright film in the same patient as shown in A. Note air–fluid levels in the small bowel (*arrows*) with little or no distal bowel gas. C: An AP supine film of postoperative ileus. Note the presence of air throughout the entire GI tract.

(Reprinted with permission from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Lippincott-Raven, 1998:157, Figure 8-20A and C, and 156, Figure 8-19A.)

Paralytic Ileus

- Peristalsis is decreased or absent (no mechanical obstruction is present).
- Causes include medications (e.g., opioids, drugs with anticholinergic effects), postoperative state (after abdominal surgery), spinal cord injury, intraabdominal inflammation, metabolic disorders (especially hypokalemia), and peritonitis.
- Abdominal plain films show a uniform distribution of gas in the small bowel, colon, and rectum (in contrast to small bowel or colonic obstruction). CT abdomen can be useful to distinguish between ileus and bowel obstruction.
- Failure to pass contrast medium beyond a fixed point is diagnostic.
- Treatment involves IV fluids, NPO, correction of electrolyte imbalances (especially hypokalemia), nasogastric suction if necessary, and nutritional support if prolonged.

Quick HIT

Paralytic ileus resolves with time or when the underlying cause is addressed medically. Surgery is usually not needed.

Celiac Disease

- Characterized by hypersensitivity to gluten (in wheat products)
- Risk factors include first- and second-degree relatives with celiac disease, and other autoimmune conditions (type 1 diabetes, autoimmune thyroiditis)
- Results in diarrhea (most common symptom), weight loss, abdominal distention, bloating, weakness, and fatigue
- Patients may suffer from vitamin deficiency secondary to fat malabsorption, leading to osteoporosis (vitamin D deficiency), easy bleeding (vitamin K deficiency), and megaloblastic anemia (secondary to impaired folate and vitamin B_{12} absorption)
- **Dermatitis herpetiformis (papulovesicular lesion seen on the extensor surfaces) is found in 10% to 20% of patients with celiac disease**
- Diagnosis is made by serologic antibodies (antitissue transglutaminase, antiendomysial, or antigliadin antibody)

- Biopsy in proximal small bowel reveals flattening of villi, which causes malabsorption.
- Strict adherence to a gluten-free diet is essential

Whipple’ Disease

- Rare disease caused by infection by the bacterium *Tropheryma whipplei.*
- Inflammation secondary to the infection damages villi in the small intestine
- Weight loss, diarrhea, joint pain, and arthritis are common symptoms but clinical presentation is extremely variable.
- Diagnosis is made by visualization of **periodic acid-Schiff stain (PAS)–positive macrophages in the lamina propria containing non–acid-fast gram-positive bacilli.**
- Treatment is with antibiotic therapy for 1 to 2 years.

Tropical Sprue

- Also known as “environmental enteropathy,” occurs in people who live in or visit tropical areas.
- Unknown etiology, believed to be caused by overgrowth of bacteria.
- Similar symptoms to celiac sprue including weight loss, diarrhea, cramps, fatigue, malabsorption.
- Abnormal flattening of villi can be observed during endoscopy.
- Treat with antibiotics and folic acid for 6 months or longer.

Inflammatory Bowel Disease

Crohn Disease

A. General Characteristics

1. Crohn disease is a chronic transmural inflammatory disease that can affect any part of the GI tract (mouth to anus) but most commonly involves the small bowel (terminal ileum).

2. Distribution: There are three major patterns of disease:
   a. 80% of patients have small bowel disease, usually in distal ileum
   b. 50% of patients have disease in both the ileum and colon
   c. 20% of patients have disease confined to the colon.
   d. Rarely, other parts of GI tract may be involved (stomach, mouth, esophagus).

Quick HIT

Epidemiology of IBD

- More common in White populations than other groups
- Particularly common in Jewish populations
- Mean age of onset is 15 to 35 years

3. Pathology
   a. **Terminal ileum is the hallmark location**, but other sites of GI tract may also be involved
   b. Skip lesions—discontinuous involvement
   c. Fistulae
   d. Luminal strictures
   e. Noncaseating granulomas
   f. Transmural thickening and inflammation (full-thickness wall involvement)—results in narrowing of the lumen
   g. Mesenteric "fat creeping" onto the antimesenteric border of small bowel

CLINICAL PEARL 3-8

Extraintestinal Manifestations of IBD

- Eye lesions
- Episcleritis—parallels bowel disease activity
- Anterior uveitis—independent course
- Skin lesions
- Erythema nodosum—especially in Crohn disease; parallels bowel disease activity
- Pyoderma gangrenosum—especially in UC; parallels bowel disease activity in 50% of cases
- Arthritis—most common extraintestinal manifestation of IBD
- Migratory monoarticular arthritis—parallel bowel disease activity (coincides with exacerbation of colitis)
- Ankylosing spondylitis—patients with UC have a 30 times greater incidence of ankylosing spondylitis than the general population; the course is independent of the colitis.
- Sacroiliitis—does not parallel bowel disease activity
- Thromboembolic hypercoagulable state—can lead to deep venous thrombosis (DVT), pulmonary embolism (PE), or a cardiovascular accident (CVA)
- Idiopathic thrombocytopenic purpura
- Osteoporosis
- Gallstones in Crohn disease (ileal involvement)
- Sclerosing cholangitis in UC

B. Clinical Features

1. Diarrhea (sometimes with blood)
2. Malabsorption and weight loss (common)
3. Crampy abdominal pain (usually RLQ), nausea, and vomiting
4. Fever, malaise
5. Extraintestinal manifestations in 15% to 20% of cases (uveitis, arthritis, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, aphthous oral ulcers, cholelithiasis, and nephrolithiasis) (see also Clinical Pearl 3-8)

Quick HIT

Crohn disease has a chronic, indolent course characterized by unpredictable **flares and remissions.** The effectiveness of medical treatment decreases with advancing disease, and complications eventually develop, requiring surgery. There is no cure, and recurrence is common even after surgery.

C. Diagnosis

1. Endoscopy (sigmoidoscopy or colonoscopy) with biopsy—typical findings are aphthous ulcers, cobblestone appearance, pseudopolyps, patchy (skip) lesions.
2. Small bowel imaging with MRI or CT with enterography (uses a contrast agent to distend small bowel for visualization)
3. Upper GI with small bowel follow-through is an option if MRI/CT cannot be done

D. Complications

1. Fistulas—between colon and other segments of intestine (enteroenteral), bladder (enterovesical), vagina (enterovaginal), and skin (enterocutaneous)
2. Anorectal disease (in 30% of patients)—fissures, abscesses, perianal fistulas
3. SBO (in 20% to 30% of patients) is the most common indication for surgery
   a. Initially, it is due to edema and spasm of bowel with intermittent signs of obstruction; later, scarring and thickening of bowel cause chronic narrowing of lumen
4. Malignancy—increased risk of colonic and small bowel tumors (but less common than risk of malignancy in UC)
5. Malabsorption of vitamin B_{12} and bile acids (both occur in terminal ileum).
6. Cholelithiasis may occur secondary to decreased bile acid absorption
7. Nephrolithiasis—increased colonic absorption of dietary oxalate can lead to calcium oxalate kidney stones
8. Aphthous ulcers of lips, gingiva, and buccal mucosa (common)
9. Toxic megacolon—less common in Crohn disease than in UC

10. Delayed growth
11. Opioid use disorder, psychosocial issues due to chronicity and progressive nature of disease

Quick HIT

Patients may have vague abdominal pain and diarrhea for years before a diagnosis of Crohn disease is considered.

E. Treatment

1. Medical
   a. Systemic corticosteroids (prednisone)—used as initial therapy for low-risk patients with diffuse disease or left-sided colon disease. Attempt taper when clinically improved. If unable to taper, consider immunosuppressant or biologic agent (below)
   b. Budesonide—used in low-risk patients with mild disease in ileum or right colon. Attempt taper when clinically improved. If unable to taper, consider immunosuppressant or biologic agent (below).
   c. Biologic agent (TNF inhibitor, e.g., infliximab, adalimumab) can be used as monotherapy or in combination with immunomodulator therapy (azathioprine, 6-mercaptopurine, or methotrexate) in patients with moderate to severe disease.
2. Surgical (eventually required in most patients)
   a. Reserved for complications of Crohn disease or for those who have persistent symptoms despite best medical management
   b. Involves segmental resection of involved bowel
   c. Disease recurrence after surgery is high. Up to 50% of patients experience endoscopic disease recurrence at 1 year postoperatively.
   d. Indications for surgery include SBO, fistulae (especially between bowel and bladder or vagina), disabling disease, and perforation or abscess.
3. Nutritional supplementation and support—parenteral nutrition is sometimes necessary.

Ulcerative Colitis

A. General Characteristics

1. UC is a chronic inflammatory disease of the colon or rectal mucosa (see also Table 3-8).
2. It may occur at any age (usually begins in adolescence or young adulthood).
3. Distribution: **UC involves the rectum in all cases** and can involve the colon either partially or entirely, but is always continuous. There are **no skip lesions** as are seen in Crohn disease.
   a. Rectum alone (in 10% of cases)
   b. Rectum and left colon (in 40% of cases)
   c. Rectum, left colon, and right colon (in 30% of cases)
   d. Pancolitis (in 30% of cases)
   e. The small bowel is not usually involved in UC, but it may reach the distal ileum in a small percentage of patients (“backwash ileitis” in 10% of cases)
4. The course is unpredictable and variable and is characterized by periodic exacerbations and periods of complete remission. Less than 5% of patients have an initial attack without any recurrence.
5. Pathology
   a. Uninterrupted involvement of rectum and/or colon
   b. Inflammation is not transmural (as it is in Crohn disease). It is limited to the mucosa and submucosa
   c. PMNs accumulate in the crypts of the colon causing crypt abscesses

TABLE 3-8 Crohn Disease Versus Ulcerative Colitis

	Crohn Disease	Ulcerative Colitis
Involvement	Transmural—intestinal wall from mucosa to serosa	Mucosa and submucosa
	Discontinuous involvement (skip lesions)	Continuous involvement (no skip lesions)
Location	Terminal ileum (most common)	Confined to colon and rectum
	Can involve any part of the GI tract (resection is not curative—recurrences occur)	Colectomy is curative
Complications	Fistulae and abscesses are more common than in UC because the entire wall is involved	SC and colorectal cancer are more common than in Crohn disease

Quick HIT

Patients with UC may have nonbloody diarrhea at first, with eventual progression to bloody diarrhea.

B. Clinical Features (wide ranges of presentation are seen)

1. **Hematochezia (bloody diarrhea)**
2. **Colicky abdominal pain**
3. Bowel movements are frequent but small
4. Fever, anorexia, and weight loss (severe cases)
5. Tenesmus (rectal dry heaves) and rectal urgency
6. Extraintestinal symptoms (e.g., jaundice, uveitis, arthritis, skin lesions) —see Clinical Pearl 3-8

C. Diagnosis: perform the following initial studies

1. Stool cultures for common infectious pathogens (*Clostridium difficile, Salmonella, Shigella, Campylobacter, Yersinia, E. coli),* stool ova and parasites, and *Giardia* stool antigen to rule out infectious diarrhea
2. Fecal leukocytes

   a. WBCs can appear in IBD, ischemic colitis, or infectious diarrhea
3. Colonoscopy to assess the extent of disease and the presence of any complications

D. Complications

1. Bleeding and iron-deficiency anemia
2. Electrolyte disturbances and dehydration secondary to diarrhea
3. Fulminant colitis and toxic megacolon (can lead to perforation)
4. Strictures, benign and malignant (usually malignant)
5. Colon cancer—The risk correlates with extent and duration of colitis. In distal proctitis there is no increased risk of CRC.
6. Sclerosing cholangitis (SC)—Does not correlate with bowel disease and is not prevented by colectomy.
7. Cholangiocarcinoma
8. Delayed growth
9. Opioid use disorder, psychosocial issues due to chronicity and progressive nature of disease

E. Treatment

1. Medical (Figure 3-15)
   a. Mesalamine or sulfasalazine (topical application as a suppository)—the mainstay of treatment. Preferred over topical steroids and can be used as maintenance therapy or induction therapy in mild to moderate disease.
      - It is effective in maintaining remissions. 5-ASA (mesalamine) is the active component.
      - 5-ASA enemas can be used for proctitis and distal colitis.

   b. Oral glucocorticoids—used when patients fail to respond to topical and oral 5-ASA therapy (above). If adequate clinical response is achieved, attempts to taper off of glucocorticoids should occur after 2 to 4 weeks. Can be used in conjunction with 5-ASA (topical and oral) for patients with severe colitis.

   c. TNF inhibitors (e.g., infliximab, adalimumab) and thiopurines (6-mercaptopurine, azathioprine) can be used in patients who do not respond to corticosteroids or for severe disease.

d. Other biologics (e.g., vedolizumab, ustekinumab) can be used to induce remission for moderate or severe disease.

Quick HIT

Sulfasalazine is metabolized by bacteria to 5-ASA and sulfapyridine. 5-ASA is the effective moiety of the drug, and sulfapyridine causes the side effects.

2. Surgical—often curative (unlike Crohn disease) and involves total colectomy. Indications for surgery include:
   a. Severe disease that is debilitating, refractory, and unresponsive to medical therapy
   b. Toxic megacolon (risk of perforation), obstruction (due to stricture), severe hemorrhage, perforation
   c. Fulminant exacerbation that does not respond to steroids
   d. Evidence of colon cancer or increased risk of colon cancer
   e. Growth failure or failure to thrive in children
   f. Systemic complications

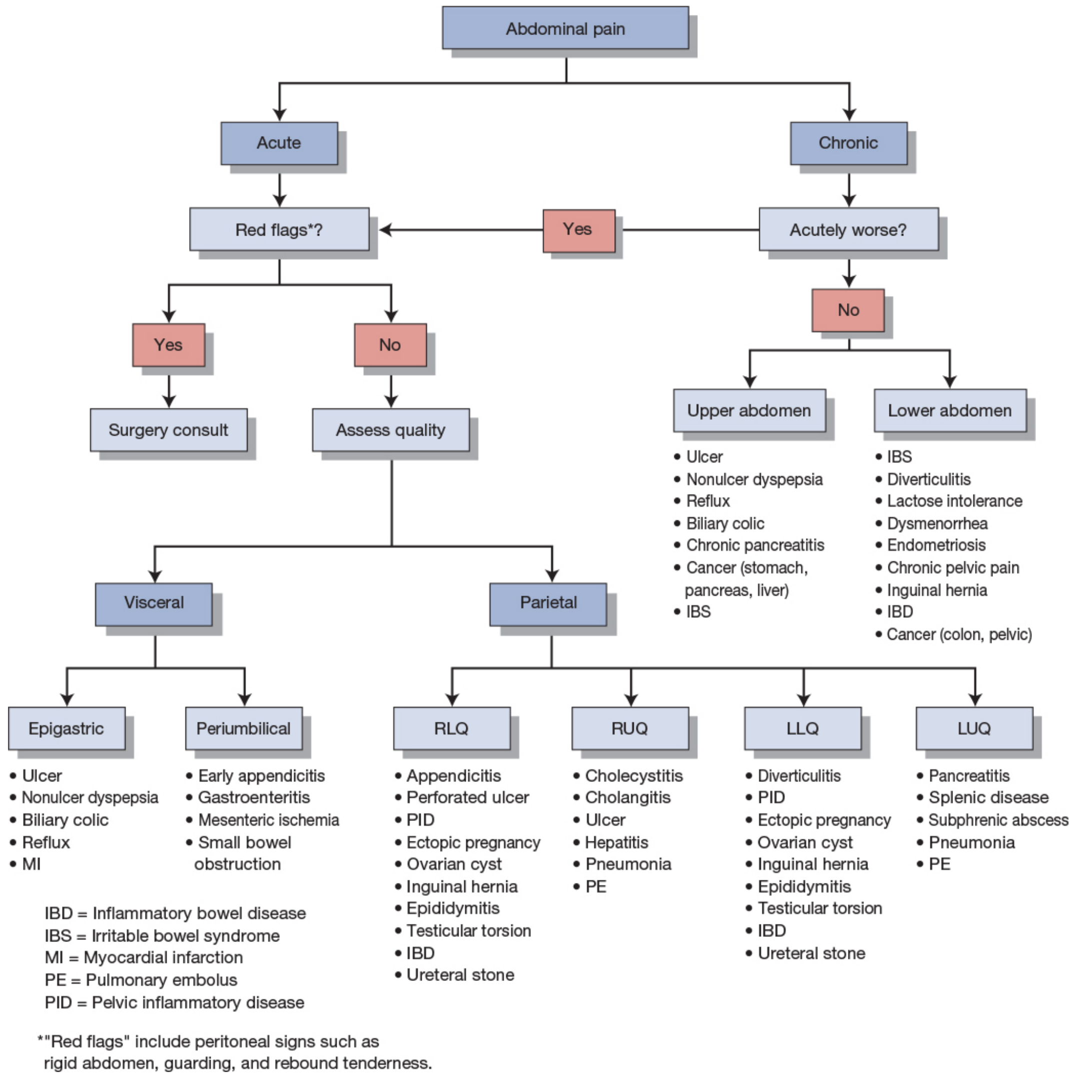


FIGURE 3-15 Approach to the diagnosis of nontraumatic abdominal pain in adults.

(Adapted with permission from Sloane PD, Slatt LM, Ebell MH, et al. *Essentials of Family Medicine*. 4th ed. Lippincott Williams & Wilkins; 2002:245. Figure 16.2.)

Endocrine and Metabolic Diseases

4

Kelley Chuang

Diseases of the Pancreas

Diabetes Mellitus

A. General Characteristics

1. Classification (see also Table 4-1)
   a. Type I DM—approximately 5% to 10% of all diabetic patients
      - This is characterized by a severe deficiency of insulin. Patients require insulin to live
      - The onset is typically in youth (before age 20), but can occur at any age
      - Often presents initially as diabetic ketoacidosis (DKA)
      - Not related to obesity
   b. Type II DM—90% or more of all diabetic patients
      - Insulin levels may initially be normal but diminish over many years, leading to insulin deficiency
      - Insulin resistance due to obesity plays a major role
      - DKA is less common but can still occur. Hyperosmolar hyperglycemic state (HHS) may occur during times of stress
      - It often goes undiagnosed for many years
   c. Impaired fasting glucose
      - Fasting glucose between 100 and 125 mg/dL or a 2-hour glucose between 140 and 199 mg/dL after a 75-g oral glucose tolerance test
      - Hemoglobin A1c between 5.7% and 6.4%

- One to five percent annual increase in risk of developing type II diabetes
- Increased risk for cardiovascular disease

2. Pathogenesis of type I diabetes (see also Clinical Pearls 4-1 and 4-2)
   a. An autoimmune disease—The immune system mediates the destruction of insulin-producing β-cells in islets of Langerhans
   b. It develops in genetically susceptible individuals who are exposed to an environmental factor that triggers the autoimmune response; β-cell destruction ensues
   c. Overt type I DM does not appear until about 90% of β-cells are destroyed
3. Pathogenesis of type II diabetes
   a. Risk factors
      - Obesity (greatest risk factor)
      - Family history
      - Age (insulin production decreases with age)
      - Sedentary lifestyle
      - Dietary factors (red meat, processed foods, sugary beverages)
   b. Obesity plays a major role, especially abdominal obesity
      - Obesity is associated with increased plasma levels of free fatty acids, which make muscles more insulin resistant, reducing glucose uptake. **Therefore, obesity exacerbates insulin resistance**
      - In the liver, free fatty acids increase the production of glucose
   c. Lack of compensation in type II diabetic patients
      - In normal individuals, the pancreas secretes more insulin in response to free fatty acids, thus neutralizing the excess glucose
      - In type II diabetic patients, free fatty acids fail to stimulate pancreatic insulin secretion. Therefore, compensation does not occur and hyperglycemia develops; β-cells become desensitized to glucose, leading to decreased insulin secretion

Quick HIT

Hypertriglyceridemia with HDL depletion is the characteristic lipid profile of insulin resistance and poorly controlled diabetes.

Quick HIT

Diabetes is diagnosed by **one** of the following:

1. Two fasting glucose measurements ≥126 mg/dL
2. Single random glucose level ≥200 mg/dL with symptoms, with repeat confirmation
3. Two-hour 75-g oral glucose tolerance test with glucose ≥200 mg/dL, with repeat confirmation
4. Hemoglobin A1c ≥6.5%

TABLE 4-1 Comparison of Type I and II Diabetes Mellitus

	Type I	Type II
Onset	Sudden	Gradual
Age at Onset	Any age (typically young)	Mostly in adults
Body Habitus	Usually thin	Frequently obese
Ketosis	Common	Rare
Autoantibodies	Present in most cases	Absent
Endogenous Insulin	Low or absent	Can be normal, decreased, or increased
HLA Association	**Yes (HLA-DQ/DR)**	**No**
Genetic Factors	Concordance rate between identical twins is 50%.	Concordance rate between identical twins is 90%. Therefore, type II demonstrates a much stronger genetic component than type I.

CLINICAL PEARL 4-1

Dawn Phenomenon and Somogyi Effect

- The dawn phenomenon is morning hyperglycemia thought to be due to an increase in the nocturnal secretion of growth hormone. It can occur regardless of nocturnal glucose levels.
- The Somogyi effect has since been refuted by clinical studies. It proposed that morning hyperglycemia was a rebound response to nocturnal hypoglycemia—that is, counterregulatory systems are activated in response to hypoglycemia, leading to morning hyperglycemia.
- In clinical practice, morning hyperglycemia is common in both types I and II diabetes and can be difficult to control. It is not associated with nocturnal hypoglycemia.

CLINICAL PEARL 4-2

General Principles in Outpatient Management and Monitoring of All Diabetic Patients

- Monitor HbA1c level every 3 months in poorly controlled diabetes. In those with stable glycemic management, monitor A1c at least twice yearly. Keeping HbA1c ≤7% is the objective for most patients to reduce risk for microvascular complications. A more liberal goal of <8% is reasonable for older patients, those with comorbidities, or elevated risk of hypoglycemia.
- All diabetic patients who take insulin and oral diabetes medications that can cause hypoglycemia should monitor daily glycemic levels with home blood glucose testing. Patients on insulin therapy should check blood glucose levels before meals and at bedtime. Monitoring blood glucose 90 to 120 minutes after meals enables the patient to control postprandial hyperglycemia and should be strongly encouraged.
- Screen for increased albuminuria with a spot urine albumin-to-creatinine ratio at least once per year in diabetic patients with no evidence of nephropathy.
- Prescribe ACE inhibitor or ARB if urine test is positive for increased albuminuria.
- Check a basic metabolic panel at least once per year.
- Order eye screening yearly to screen for diabetic retinopathy.
- Check the feet at every visit. Refer high-risk patients to a foot care specialist (e.g., podiatrist). Patients should check their feet regularly for ulcers and neuropathy.
- Check a lipid panel at least once per year. Give statin medication if at elevated ASCVD risk (atherosclerotic cardiovascular disease).
- Take BP at every visit. Give ACE inhibitor or ARB if BP is greater than 130/80 mmHg.
- Daily aspirin for secondary prevention in those with existing ASCVD. Benefit of daily aspirin for primary prevention is uncertain.
- Vaccinations: yearly influenza, pneumococcal (PPSV23 vaccine once before and once after age 65, plus PCV13 vaccine for age ≥65), SARS-CoV-2 vaccines.

TABLE 4-2 Diagnostic Criteria for Diabetes Mellitus

Glucose Test	Impaired Glucose Tolerance (mg/dL)	Diabetes Mellitus (mg/dL)
Random plasma	—	≥200 with diabetic symptoms
Fasting	110–126	≥126 on two occasions
2-hr postprandial	140–200	≥200 on two occasions
Hemoglobin A1c (%)	5.7–6.4	≥6.5

B. Diagnosis

1. Testing recommendations (see also Table 4-2)
   a. Screen all adults between ages 35 and 70
   b. For those with risk factors for diabetes (obesity, family history, history of gestational diabetes), start screening earlier. Some recommend early screening for African Americans and Native Americans
   c. Test anyone with signs or symptoms of diabetes
2. Perform any one of the following tests on *two separate days* (see Table 4-2)
   a. Fasting plasma glucose—criteria for DM: glucose >126 mg/dL
      - If between 100 and 126 mg/dL, perform a 75-g oral glucose tolerance test (although this is rarely done) or recheck fasting glucose
   b. Random plasma glucose—criteria for DM: glucose ≥200 mg/dL in a person with diabetic symptoms
   c. Two-hour postprandial plasma glucose level—criteria for DM: glucose ≥200 mg/dL after administration of the equivalent of a 75-g glucose load (more sensitive than fasting glucose level, but less convenient)
   d. Hemoglobin A1c—criteria for DM: A1c ≥6.5% (repeat test should occur >3 months later as opposed to the next day). Many use this as preferred screening method

C. Clinical Presentation

1. Type I (see Table 4-3 and Figure 4-1)
   a. Symptoms develop quickly over days to weeks
   b. Sometimes symptoms appear after an illness
   c. Patients often present with acute DKA
2. Type II
   a. Usually discovered on screening urinalysis or blood glucose measurement. Sometimes the diagnosis is made during evaluation for other diseases (e.g., heart, kidney, neurologic, infection)
   b. Symptomatic patients may present with polyuria, polydipsia, polyphagia, fatigue, blurred vision, weight loss, and/or candidal vaginitis. These symptoms are usually noted in retrospect, after elevated blood glucose has been documented
   c. Patients who have not routinely sought medical attention may present with complications such as myocardial ischemia, stroke, intermittent claudication, erectile dysfunction, peripheral neuropathy, nephropathy, or retinopathy

TABLE 4-3 Symptoms of Diabetes Mellitus

Symptom	Cause
Polyuria	Glucose in renal tubule causes osmotic retention of water, causing a diuresis
Polydipsia	A physiologic response to diuresis to maintain plasma volume
Fatigue	Mechanism unknown, but probably due to increased glucose in plasma
Weight loss	Due to loss of anabolic effects of insulin
Blurred vision	Swelling of lens due to osmosis (caused by increased glucose)
Fungal infections	Fungal infections of mouth and vagina common—*Candida albicans* thrives under increased glucose conditions
Numbness, tingling of hands and feet	Neuropathy Mononeuropathy: due to microscopic vasculitis leading to axonal ischemia Polyneuropathy: etiology is probably multifactorial

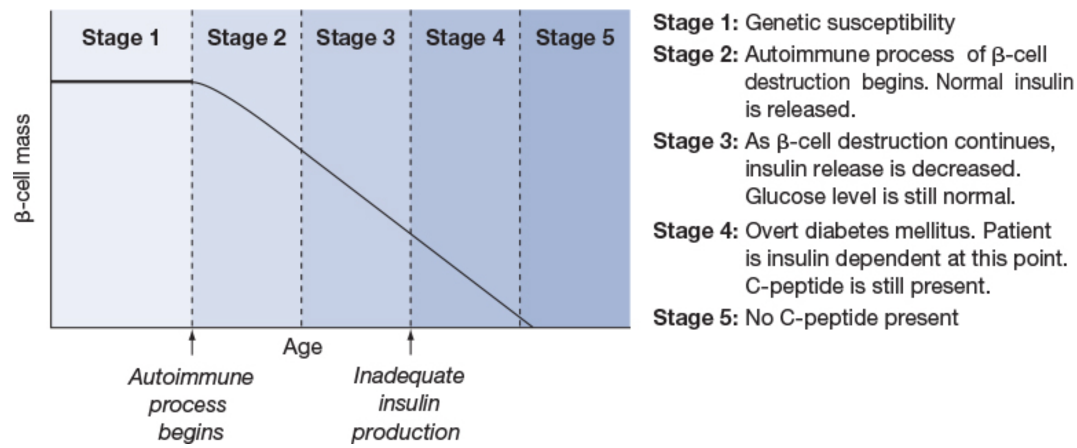


FIGURE 4-1 **Progression of type I diabetes mellitus.**

***Quick* HIT**

While evaluating a diabetic patient, focus on:

- The feet
- Vascular disease (CAD, PAD)
- Neurologic disease (neuropathies)
- Eyes (retinopathy)
- Renal disease
- Infectious disease

***Quick* HIT**

Optimal Treatment for Type II Diabetic Patients

- Glycemic control
- BP control—<130/80 mmHg
- Optimization of serum lipids—goals: LDL ≤100, HDL ≥40. Check lipids annually.
- Smoking cessation
- Daily aspirin for secondary prevention of ASCVD (benefit for primary prevention is unclear)
- Inspect feet at every visit
- Retinopathy examination yearly
- Urine albumin–creatinine ratio annually
- Measure A1c every 3 to 6 months.

D. Treatment

1. Lifestyle modification should ideally be the only interventions in most type II diabetic patients
   a. Diet and exercise are especially effective in obese and sedentary patients (who constitute the majority of type II diabetic patients)
   b. Most patients, however, will require pharmacologic treatment
   c. Glycemic control minimizes risks for nephropathy, neuropathy, and retinopathy in both type I and II DM, and decreases risk for cardiovascular disease for type I DM
2. Noninsulin diabetes medications (see Table 4-4)
   a. Use these in type II diabetic patients when conservative therapy (diet and exercise) is insufficient
   b. Start with one agent; metformin is best initial drug therapy. If monotherapy fails, use two agents from different classes in combination. Each agent has advantages and disadvantages, so clinical judgment is required in selecting the agent
   c. Metformin blocks gluconeogenesis. It should be avoided if eGFR <30 mL/min/1.73 m^2
   d. Other noninsulin diabetes medications include:
      - Sulfonylureas
      - Thiazolidinediones (glitazones)
      - GLP-1 agonists
      - DPP-4 inhibitors
      - SGLT2 inhibitors
      - Glinides
      - α-Glucosidase inhibitors (acarbose, miglitol)
   e. There are numerous studies evaluating cardiovascular benefits of SGLT2 inhibitor therapy in high-risk CVD patients
   f. In patients with relatively mild disease, use of these drugs (alone or in combination) can bring glucose levels to normal, but patients with severe disease often do not respond adequately. Therefore, many type II diabetic patients eventually require insulin (see below)
   g. Avoid agents that can cause hypoglycemia in patients who are unable to eat. Also avoid SGLT2 inhibitors while NPO (due to increased risk of euglycemic DKA)

Quick HIT

Insulin Versus Noninsulin Agents in Type II Diabetes

- If the patient has severe hyperglycemia (fasting glucose >250 mg/dL or A1c > 9%), insulin typically is the agent of choice.
- Noninsulin agents are effective in type II disease with moderate hyperglycemia (fasting glucose between 140 and 250 mg/dL).

TABLE 4-4 Noninsulin Diabetes Medications

Medication	Mechanism	Site of Action	Advantages	Side Effects
SGLT-2 inhibitors (e.g., empagliflozin, canagliflozin)	Blocking SGLT-2 sodium glucose cotransporter in the proximal convoluted tubule leading glucosuria	Kidney	Reduce body weight, may reduce cardiovascular risk, beneficial in CHF	Increased urinary infections, risk of euglycemic DKA
GLP-1 agonists (e.g., liraglutide, exenatide)	Stimulate GLP-1 receptor, which stimulates insulin secretion	Pancreas	Reduce body weight, low risk of hypoglycemia	Possible increased risk of thyroid cancer and pancreatitis
DPP4 inhibitors (e.g., saxagliptin, sitagliptin)	Inhibits DPP4 receptor, which stimulates insulin secretion	Pancreas	Weight neutral, low risk of hypoglycemia	Possible increased risk of HF (saxagliptin), high cost
Sulfonylureas (e.g., glyburide, glipizide, glimepiride)	Stimulate pancreas to produce more insulin	Pancreas	Effective Inexpensive	Hypoglycemia, weight gain
Glinides (e.g., repaglinide, nateglinide)	Stimulate pancreas to produce more insulin	Pancreas	Rapidly effective	Weight gain, risk of hypoglycemia
Metformin[a]	Enhances insulin sensitivity	Liver	May cause mild weight loss Does not cause hypoglycemia (insulin levels do not increase)	GI upset (diarrhea, nausea, abdominal pain), lactic acidosis, metallic taste
Acarbose	Reduces glucose absorption from the gut, thereby reducing calorie intake	GI tract	Low risk (does not have significant toxicity)	GI upset (diarrhea, abdominal cramping, flatulence), TID dosing
Thiazolidinediones (e.g., rosiglitazone, pioglitazone)	Reduce insulin resistance	Fat, muscle	Reduce insulin levels	Fluid retention (avoid in CHF), weight gain

Most oral hypoglycemic drugs are contraindicated in pregnancy (potentially teratogenic). Treat with insulin.

[a]Avoid metformin if estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.

Quick HIT

Treatment of Diabetes

- Type I diabetic patients require insulin at all times.
- Type II diabetic patients should be counseled on lifestyle changes (exercise and healthy diet) as the first step. Next steps include noninsulin diabetes medications. Insulin may be needed for uncontrolled diabetes to optimize hemoglobin A1c.

3. Insulin (see Table 4-5 and Figure 4-2)
   a. Method of administration
      - Self-administered by SC injection in abdomen, buttocks, arm, and leg.
      - Given intravenously for DKA and HHS
   b. Regimens
      - Most type I diabetic patients require 0.5 to 1.0 unit/kg total insulin per day to achieve acceptable glycemic control
      - Start with a conservative dose (0.2 units/kg) and adjust the regimen according to the patient's glucose levels
      - Many different regimens exist, and every patient has unique needs (see Table 4-5)
   c. Basal-bolus insulin therapy
      - Intermediate- to long-acting (basal) insulin is given once or twice daily. Short-acting insulin (bolus) is given 30 to 45 minutes before each meal, and should be adjusted according to preprandial home glucose measurements
      - The basal-bolus method has been shown to significantly decrease the incidence of diabetes complications such as retinopathy and microalbuminuria when compared to prior regimens. Patients with type I diabetes should be on basal-bolus insulin therapy. Patients with type II diabetes will often start with basal insulin, and bolus insulin will need to be added later as disease progresses
      - With bolus insulin therapy, **the risk for hypoglycemia is a serious concern**
      - Alternatively, a continuous SC infusion of basal insulin can be given via an insulin pump. Preprandial boluses are given in addition to the basal infusion

d. Premixed insulin: if the patient is unable/unwilling to use basal-bolus insulin therapy
  - Mixture of 70% NPH insulin and 30% rapid-acting insulin
  - Advantages include fewer injections and lower cost. However, dose is fixed in a ratio so less ability to vary dose of rapid-acting insulin before meals
  - Give before breakfast and before the evening meal for basal coverage
  - Give additional short-acting insulin (regular) for prandial control if necessary

e. Inpatient management of diabetic patients (sliding scale)
  - An insulin sliding scale (SSI) of regular insulin doses given according to bedside finger-stick glucose determinations is helpful in controlling blood glucose levels in the hospital setting
  - **SSI should be used in addition to a regimen of long-acting insulin. If given alone, hyperglycemia usually results**
  - Monitor blood glucose four times per day: before meals and at bedtime
  - **Once insulin therapy is started, a blood glucose goal of 140 to 180 mg/dL should be targeted for most patients**
  - If the home insulin dose is unclear, or if the patient anticipates greater requirements of insulin due to an illness, use the following approach to adjust appropriate insulin doses:
    - Take the total number of units of insulin that the patient required in 24 hours (while on the sliding scale)
    - Give 50% of total dose as basal long-acting insulin. Give the remaining 50% of total dose divided up three times a day with meals as a bolus rapid-acting insulin (if patient is eating). For example, if the patient required 30 units of insulin in the last 24 hours, can adjust to 15 units of insulin glargine (basal) and 5 units of insulin aspart (bolus) three times a day with meals

f. Modifying insulin doses (see also Clinical Pearl 4-3)
  - Physical activity—depending on the intensity of the activity, decrease insulin dosage 1 to 2 units per 20 to 30 minutes of activity

- During illness, patients on basal insulin should continue this. Bolus insulin may be held or reduced if not eating consistently. Monitoring blood sugars is vital. **Many episodes of DKA or HHS occur during episodes of illness**
- Stress and changes in diet require dosing adjustments
- Patients undergoing surgery should get 50% to 75% of the usual basal insulin requirement that day, with frequent monitoring and adjustments as necessary. Rapid-acting or bolus insulin should be held while fasting

4. Surgical treatment—Bariatric surgery (i.e., gastric bypass) is an effective treatment for some patients. In addition, islet cell transplantation offers definitive treatment for selected qualified patients, usually with end-stage complications of diabetes

TABLE 4-5 Types of Insulin

Prandial Insulin	**Onset**	**Duration**	**Comments**
Insulin aspart or lispro	15–30 min	4–6 hrs	Peaks at 1–3 hrs
Regular insulin	30 min	8 hrs	Only type that can be given IV
Basal Insulin	**Half-life**	**Duration**	**Comments**
NPH insulin	4–5 hrs	12 hrs	Intermediate-action, dosed twice daily for basal coverage
Insulin glargine	3-4 hrs	24 hrs	No pronounced peak
Insulin detemir	5-7 hrs	6-24 hrs	Duration is dose-dependent
Insulin degludec	25 hrs	>24 hrs	No pronounced peak

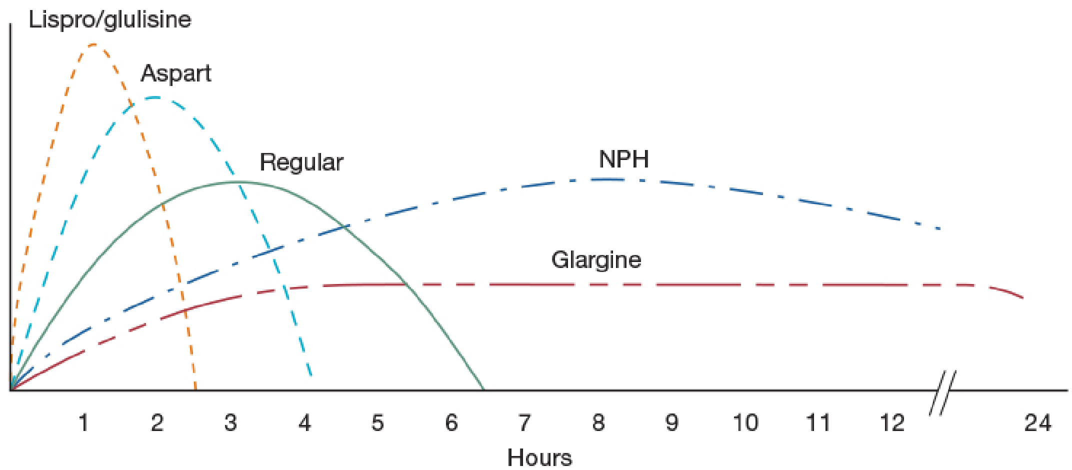


FIGURE 4-2 Onset and duration of action for common types of insulin.
(Reprinted with permission from Yao FS, Hemmings HC, Malhotra V, et al. *Yao & Artusio's Anesthesiology: Problem-oriented Patient Management*. 9th ed. Wolters Kluwer; 2020. Figure 23.1.)

CLINICAL PEARL 4-3

Monitoring Glucose Levels in DM

- HbA1c gives an estimate of the degree of glucose control over 2 to 3 months. It is less reliable in conditions that cause altered RBC turnover (such as anemia, hemolysis, and CKD). In some cases, other biomarkers such as frucostamine can be used to estimate glycemic control.
- The American Diabetes Association recommends a treatment goal for most adults of HbA1c <7.0%. A liberal goal (<8.0%) may be appropriate if the patient has advanced complications, limited life expectancy, or a history of severe hypoglycemia. In general, HbA1c >10% is poor control, 8.5% to 10% is fair control, 7.0% to 8.5% is good control, and <7.0% is ideal as long as the patient is not experiencing hypoglycemic episodes.
- The American Diabetes Association recommends keeping fasting blood glucose level between 70 and 130 mg/dL and peak postprandial blood glucose <180 mg/dL.

Chronic Complications of Diabetes Mellitus

A. Macrovascular Complications

1. The main problem is **accelerated atherosclerosis**, which puts patients at increased risk of stroke, MI, and CHF (Figure 4-3). The accelerated atherosclerosis in diabetics is the reason the target BP is strict in diabetics (<130/80) and the reason the target LDL is <100 mg/dL. The cause of accelerated atherosclerosis is not known, although glycation of lipoproteins and increased platelet adhesiveness/aggregation are thought to be two potential causes. In addition, the process of fibrinolysis may be impaired in diabetic patients
2. The manifestations of atherosclerosis include the following:
   a. Coronary artery disease (CAD)
      - Risk of CAD is twofold greater in diabetic than in nondiabetic persons
      - **Most common cause of death in diabetic patients**
      - Asymptomatic CAD and silent ischemia are common

   b. Peripheral artery disease (one third of patients with PAD in the United States also have diabetes)

   c. Cerebrovascular disease (strokes)

***Quick* HIT**

The risk of coronary events is greatly reduced if the patient can eliminate or reduce other major cardiovascular risk factors (smoking, HTN, hyperlipidemia, obesity).

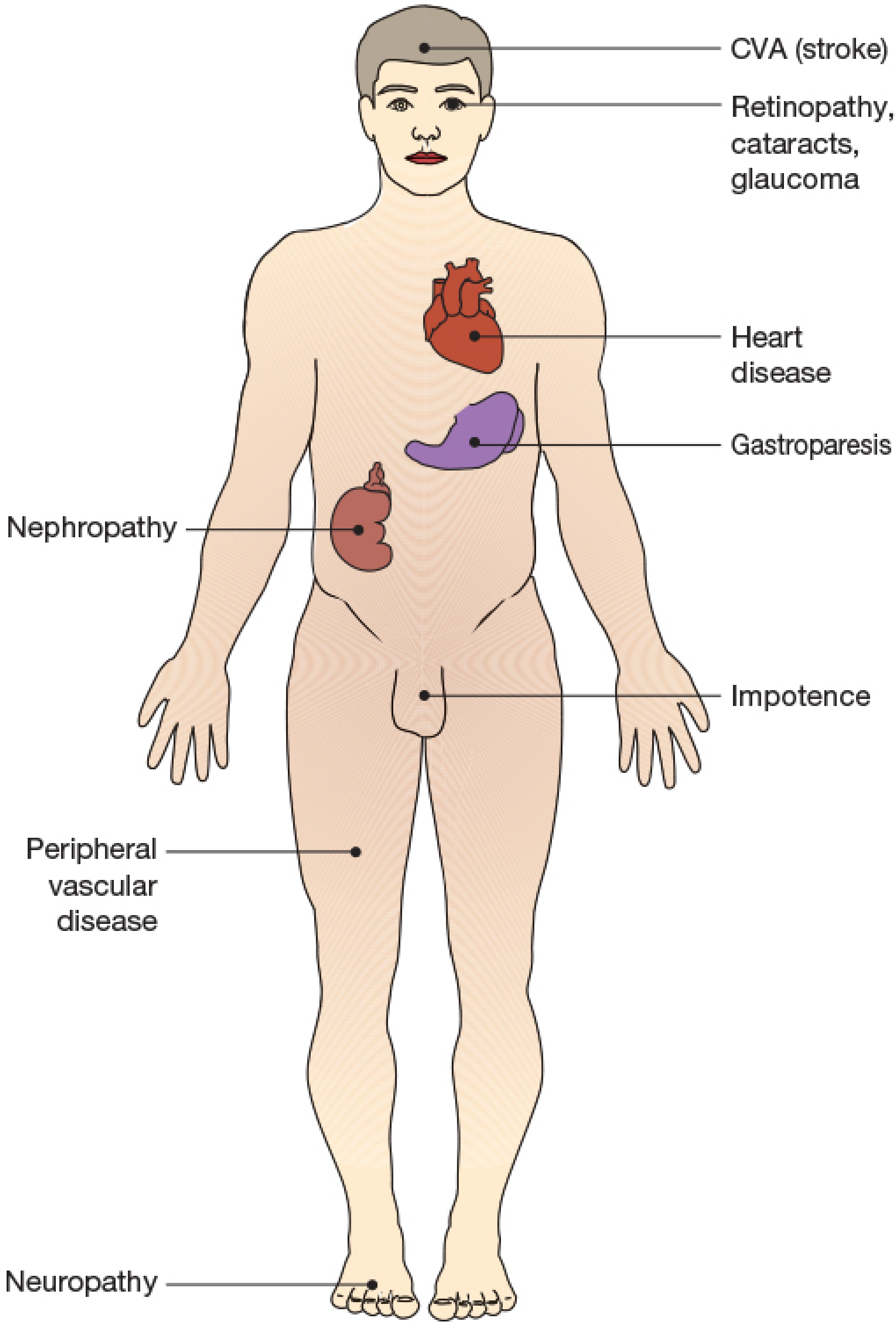


FIGURE 4-3 **Chronic complications of diabetes mellitus.**

B. Microvascular Complications

Risk can be markedly reduced by achieving tight glucose control (see also Clinical Pearl 4-4).

1. **Diabetic nephropathy**—leading cause of end-stage renal disease (ESRD)
   a. Pathologic types
   - Isolated glomerular basement membrane thickening
   - Mesiangial expansion
   - Nodular glomerular sclerosis (Kimmelstiel–Wilson syndrome)—hyaline deposition in **one** area of glomerulus—pathognomonic for DM
   - Diffuse glomerular sclerosis—hyaline deposition is global. This also occurs in HTN

   b. Albuminuria/proteinuria (see Figure 4-4)
   - If moderately increased albuminuria is present, strict glycemic control is critical. Tight blood glucose has been shown to limit progression from moderately increased albuminuria to clinical proteinuria.
   - Without effective treatment, the albuminuria gradually worsens—HTN usually develops during the transition between albuminuria and progressive proteinuria. Persistent HTN and proteinuria cause a decrease in glomerular filtration rate (GFR), leading to renal insufficiency and eventually ESRD.
   - **HTN increases the risk of progression of diabetic nephropathy to ESRD. Control BP aggressively.**
   - **Initiate ACE inhibitor or ARB immediately. These agents are proven to decrease the rate of progression of nephropathy.** Patients with diabetic nephropathy and type II diabetes should also be treated with SGLT2 inhibitors.
   - **Urine albumin to creatinine ratio is the screening test!** If you wait for a urine dipstick to be positive for protein, you have waited too long. Remember that moderately increased albuminuria means levels of albumin are between 30 and 300 mg per 24 hours. But the dipstick for urine becomes trace positive at 300 mg of protein per 24 hours (severely increased albuminuria).

- It usually takes 1 to 5 years for moderately increased albuminuria to advance to full-blown proteinuria. However, with proper treatment (i.e., using ACE inhibitors to control BP) this can be prolonged.

c. Once diabetic nephropathy has progressed to the stage of proteinuria or early renal failure, glycemic control does not significantly influence its course. ACE inhibitors are recommended.

CLINICAL PEARL 4-4

Strict Glycemic Control

- Improved glycemic control lowers the risk of microvascular complications (retinopathy, nephropathy, and neuropathy).
- However, this must be balanced against the risk of hypoglycemia.

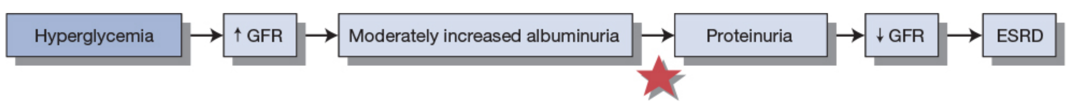


FIGURE 4-4 Progression in diabetic nephropathy. Strict glycemic control has been shown to slow or prevent progression from moderately increased albuminuria to proteinuria. This is the critical stage (marked by *star*)—once proteinuria develops, glycemic control does little to control the course and will eventually lead to ESRD.

Quick HIT

Definitions of Albuminuria

- Albumin excretion between 30 and 300 mg/day is called moderately increased albuminuria (formerly known as “microalbuminuria”)
- Albumin excretion >300 mg/day is called severely increased albuminuria (formerly known as “macroalbuminuria,” or dipstick positive proteinuria).

2. **Diabetic retinopathy**

a. Occurs in nearly everyone with diabetes and is a leading cause of blindness. **Annual screening of all diabetic patients with a dilated fundus examination or retinal photography is recommended.**

b. Background (nonproliferative) retinopathy accounts for the majority of cases.
   - Funduscopic examination shows hemorrhages, exudates, microaneurysms, and venous dilatation.
   - These patients are usually asymptomatic unless retinal edema or ischemia involves the central macula.
   - Edema of the macula is the leading cause of visual loss in diabetic patients.

c. HTN and fluid retention exacerbate this condition.

d. Proliferative retinopathy
   - Key characteristics are new vessel formation (neovascularization) and scarring.
   - Two serious complications are vitreous hemorrhage and retinal detachment.
   - **Can lead to blindness. Laser photocoagulation in combination with anti-VEGF agents (vascular endothelial growth factor inhibitors) is the treatment.**

Quick HIT

Ocular problems in diabetic patients include cataracts, retinopathy, and glaucoma. Diabetic retinopathy is the leading cause of blindness in the United States.

Quick HIT

The Diabetes Control and Complications Trial showed that tight glucose control reduces the risk of microvascular disease by 50% to 60%. However, whether it can reduce the risk of macrovascular disease remains to be proven. It is the macrovascular complications that cause death in the majority of type II diabetic patients.

3. **Diabetic neuropathy** (Figure 4-3)

   a. Peripheral neuropathy (distal symmetric neuropathy)

- Usually affects sensory nerves in a "stocking/glove pattern"—Typically begins in feet, later involves hands (longest nerves affected first). Numbness and paresthesias are common.
- Loss of sensation leads to the following: ulcer formation (patients do not shift their weight) with subsequent ischemia of pressure point areas; *Charcot joints.*
- Painful diabetic neuropathy—hypersensitivity to light touch; severe "burning" pain, especially at night, that can be difficult to tolerate. Treatment is with gabapentin, pregabalin, SNRIs, or tricyclic antidepressants.

b. Mononeuropathies and polyradiculopathies—secondary to nerve infarction.
- Cranial mononeuropathy—most commonly, CN III, but may also involve CNs VI and IV. Patients typically present with unilateral eye pain, diplopia, ptosis, and inability to adduct the eyes, but the **pupils are spared**.
- Median nerve neuropathy, ulnar neuropathy, common peroneal neuropathy.
- Diabetic lumbosacral plexopathy—severe, deep pain in the thigh; atrophy and weakness in thigh and hip muscles; recovery takes weeks to months.
- Diabetic truncal neuropathy—pain in distribution of one of the intercostal nerves.

c. Autonomic neuropathy
- Erectile dysfunction or dyspareunia
- Neurogenic bladder—retention, incontinence
- Gastroparesis—chronic nausea and vomiting, early satiety
- Constipation and diarrhea (alternating)
- Tachycardia and orthostatic (postural) hypotension

FIGURE 4-5 Foot ulcer in a patient with diabetic peripheral neuropathy.
(Reprinted from Shein S. *Clinical Medicine for Optometrists*. Wolters Kluwer; 2020. Adapted with permission from Zgonis T. *Surgical Reconstruction of the Diabetic Foot and Ankle*. 2nd ed. Wolters Kluwer; 2017. Figure 6.1.)

4. **Diabetic foot ulcer** (see Figure 4-5)
   a. Caused by a combination of artery disease (ischemia) and nerve disease (neuropathy)—can lead to ulcers/infections and may require amputation.
   b. With neuropathy, the patient does not feel pain, so repetitive injuries go unnoticed and ultimately lead to nonhealing.
   c. In addition, neuropathy may mask symptoms of PAD (claudication/rest pain). Also, calcific medial arterial disease is common and can cause erroneously high BP readings in lower extremities.
5. Increased susceptibility to infection
   a. This results from impaired WBC function, reduced blood supply, and neuropathy. Wound healing is impaired in diabetic patients, and this can be problematic postoperatively.

b. Diabetic patients are at increased risk for the following infections: cellulitis, candidiasis, pneumonia, osteomyelitis, and polymicrobial foot ulcers.
c. Infections of ischemic foot ulcers may lead to osteomyelitis and may require amputation.

C. Specific Treatment of Chronic Diabetic Complications

1. Macrovascular disease—treatment involves reduction of risk factors (e.g., BP reduction, lipid-lowering agents, smoking cessation, exercise), a daily aspirin for secondary prevention of ASCVD, and strict glycemic control.
2. Nephropathy—ACE inhibitors/ARBs and SGLT2 inhibitors, benefits of which include:
   a. Slow progression of moderate increased albuminuria to proteinuria.
   b. Slow decline of GFR.
3. Retinopathy—Treatment involves referral to an ophthalmologist and possible photocoagulation and/or anti-VEGF agents.
4. Neuropathy—Treatment is complex. Pharmacologic agents that may be helpful include gabapentinoids and antidepressants (SNRIs and TCAs). For gastroparesis, a promotility agent such as metoclopramide can be helpful, in addition to exercise and a low-fat diet.
5. Diabetic foot ulcer—The best treatment is prevention: regular foot care, **regular podiatrist visits.** Amputation is a last resort.

Acute Complications of Diabetes Mellitus

A. Diabetic Ketoacidosis

1. General characteristics
   a. DKA is an acute, life-threatening medical emergency that can occur in both type I and type II diabetic patients (more common in type I).
   b. Pathogenesis
      - This is secondary to insulin deficiency and glucagon excess, both of which contribute to accelerated severe hyperglycemia and accelerated ketogenesis.
      - Severe hyperglycemia leads to an osmotic diuresis, which causes dehydration and volume depletion.

c. Consequences of DKA include hyperglycemia, ketonemia, metabolic acidosis, and volume depletion.

2. **Precipitating factors**
   a. Any type of stress or illness (e.g., infectious process, trauma, myocardial infarction, stroke, recent surgery, sepsis, GI bleeding)
   b. Inadequate administration of insulin
   c. New-onset diabetes
   d. Drugs (cocaine, SGLT2 inhibitors, atypical antipsychotics)

***Quick* HIT**

Key Features of DKA

- Hyperglycemia (although euglycemic DKA may also occur)
- Positive serum or urine ketones
- Metabolic acidosis

3. **Clinical features**
   a. Nausea and vomiting
   b. Kussmaul respiration—rapid, deep breathing
   c. Abdominal pain (more common in children) that may mimic acute abdomen—often with guarding and rigidity
   d. “Fruity” (acetone) breath odor
   e. Marked dehydration, orthostatic hypotension, tachycardia—volume depletion is always present
   f. Polydipsia, polyuria, polyphagia, weakness
   g. Altered consciousness, drowsiness, and frank coma may occur if not treated
   h. Symptoms usually occur rapidly, typically in less than 24 hours

4. **Diagnosis**
   a. Hyperglycemia: serum glucose typically >350 mg/dL and <500 mg/dL (in certain conditions, e.g., poor oral intake, or treatment with SGLT2 inhibitors, the patient may be euglycemic)
   b. Metabolic acidosis
      - Blood pH <7.3 and serum HCO_3^- <15 to 18 mEq/L
      - Increased anion gap—due to production of ketones (acetoacetate and β-hydroxybutyrate)

c. Ketonemia (serum positive for ketones) and ketonuria

- Serum levels of acetoacetate, acetone, and β-hydroxybutyrate are greatly increased.
- When DKA is accompanied by circulatory collapse, serum and urine may be **falsely negative** for ketones. This is because lactate production results in less acetoacetate and more β-hydroxybutyrate production, and acetoacetate is the only ketoacid that can be measured by nitroprusside agents.

d. Ketonemia and acidosis are required for the diagnosis of DKA

Quick HIT

Differential Diagnosis of DKA

- Alcoholic or fasting ketoacidosis
- Hyperosmolar hyperglycemic syndrome (HHS)
- Hypoglycemia (altered mental status, abdominal pain, and acidosis are possible)
- Sepsis or other causes of anion gap metabolic acidosis
- Intoxication (e.g., methanol, ethanol, salicylates, isopropyl alcohol, paraldehyde, ethylene glycol)

5. **Other laboratory value abnormalities**

a. Hyperosmolarity

b. Hyponatremia—Serum sodium decreases 1.6 mEq/L for every 100 mg/dL increase in glucose level because of the osmotic shift of fluid from the ICF to the ECF space. Total body sodium level is normal. Sodium levels will normalize with treatment of hyperglycemia.

c. Other electrolyte disturbances

- Potassium—Because of the acidosis, hyperkalemia may be present initially, although total body potassium is low. **As insulin is given, it causes a shift of potassium into cells, resulting in a hypokalemia. This can happen very rapidly.** Phosphate and magnesium levels may also be low.

Quick HIT

If a patient presents with DKA:
- Take a history and perform a physical examination.
- Order laboratory tests: blood glucose, arterial blood gas, CBC, electrolytes, BUN, creatinine, and urinalysis.
- Order ECG, CXR, and cultures.
- Initiate IV fluids for volume resuscitation.
- **If K is <3.3 mEq/L, hold insulin** and give 20 to 40 mEq/hr until serum K is >3.3. If K is 3.3 to 5.3, give potassium with IV fluids to maintain a goal of 4 to 5 mEq/L in serum. If K >5.3, do not give any with IVF, but continue to monitor every 2 hours.
- Give IV insulin (hold if K <3.3 as above).
- Admit to the ICU or a unit where sugars can be monitored frequently (e.g., every hour).

6. **Treatment**
   a. Insulin
   - Give insulin immediately after the diagnosis is established.
   - Give a priming dose of 0.1 units/kg of regular insulin (IV) followed by an infusion of 0.1 units/kg/hr. This is sufficient to replace the insulin deficit in most patients. **Be certain that the patient is not hypokalemic before giving insulin.**
   - Continue the insulin **until the anion gap closes** and metabolic acidosis is corrected, then begin to decrease the insulin. Give SC insulin when the patient starts eating again. Continue IV insulin infusion for 2 to 4 hours after SC insulin is begun to ensure plasma insulin levels are maintained.

   b. Fluid replacement with balanced crystalloid (normal saline or lactated Ringer’s)
   - Give fluids immediately after the diagnosis is established.
   - Add 5% dextrose once the blood glucose reaches **200 mg/dL** to prevent hypoglycemia.

   c. Replace potassium prophylactically with IV fluids.
   - Ensure adequate renal function (measure urine output) before administering potassium.
   - Monitor potassium, magnesium, and phosphate levels **very closely** and replace as necessary.

d. HCO_3^- replacement is controversial and is not necessary in most cases.

Quick HIT

Treatment of DKA: **insulin, fluids, potassium. Only initiate insulin once serum K >3.3 mEq/L.**

Quick HIT

Complications of Treatment of DKA

- Cerebral edema—if glucose levels decrease too rapidly in patients who are hyperosmolar
- Hyperchloremic nongap metabolic acidosis—due to rapid infusion of a large amount of saline

A 24-year-old woman presents with labored breathing and abdominal pain. She endorses polydipsia and polyuria. She has a blood pressure of 130/90 mmHg, her pulse is 120 beats per minute, and her respiratory rate is 24 breaths per minute. Laboratory results reveal the following.

Sodium	134 mEq/L
Potassium	3.9 mEq/L
Chloride	94 mEq/L
Bicarbonate	16 mEq/L
Creatinine	1.0 mg/dL
Glucose	880 mg/dL

She is treated with intravenous insulin and isotonic saline solution. Two hours later her serum glucose concentration is 410 mg/dL with ample urine output.

Which of the following is the most appropriate next step?

A. Add glucose to the IV solution
B. Add potassium to the IV solution
C. Initiate treatment with intermediate-acting insulin
D. Discontinue isotonic saline solution and begin hypotonic saline solution

- **The answer is B: Add potassium to the IV solution.** The patient in this question is presenting in DKA. Since insulin causes an intracellular shift of potassium, potassium should be added to the replacement solution (10 to 20 mEq/L) once urine output is ample and the serum potassium is <5.3–5.5 mEq/L. **(A)** Glucose should only be added once blood glucose reaches 200 mg/dL. **(C)** Intermediate-acting insulin can be given instead of continuous IV insulin once the anion gap has been corrected and the patient can

tolerate PO intake. **(D)** Hypotonic saline solution has no role in the treatment of DKA.

B. Hyperosmolar Hyperglycemic Syndrome (HHS)

1. **General characteristics** (see also Table 4-6)
   a. A state of severe hyperglycemia, hyperosmolarity, and dehydration is typically seen in type II diabetic patients.
   b. Pathogenesis
      - Low insulin levels lead to hyperglycemia. Severe hyperglycemia causes an osmotic diuresis, leading to dehydration.
      - Ketogenesis is minimal because a small amount of insulin is released to blunt counterregulatory hormone release (glucagon), and thus ketones are not produced in excess as they are in DKA.
      - Ketosis and acidosis are typically absent or minimal.
      - Severe dehydration is due to continued hyperglycemic (osmotic) diuresis. The patient's inability to drink enough fluids (either due to lack of access in elderly/bedridden patients or to an inadequate thirst drive) to keep up with urinary fluid losses exacerbates the condition.
   c. Precipitating events are similar to those of DKA.

TABLE 4-6 Diabetic Ketoacidosis Versus Hyperosmolar Hyperglycemic Syndrome

	DKA	HHS
Pathophysiology	Insulin deficiency → ketosis, acidosis, dehydration	Insulin deficiency → hyperosmolarity, osmotic diuresis, profound dehydration
Laboratory Findings	• Hyperglycemia (>350), although glucose may be normal in euglycemic DKA • Metabolic acidosis (anion gap)—serum pH <7.3 • Ketosis	• Hyperglycemia (>600 mg/dL) • Hyperosmolarity (>320 mOsm/L) • Serum pH >7.3 (no acidosis)
Treatment	Insulin, IV fluids, potassium	IV fluids, low-dose insulin infusion, potassium
Mortality Rate	5–10%	10–20%

Quick HIT

A number of names have been used for this clinical entity, including hyperosmolar hyperglycemic nonketotic state (HHNS), hyperosmolar hyperglycemic nonketotic coma (HHNC), and hyperosmolar nonacidotic diabetes.

Quick HIT

HHS has a higher mortality rate than DKA, but it is less common than DKA. This may be because many HHS patients are elderly with other comorbid conditions (e.g., heart, renal, or pulmonary disease).

2. **Clinical features**
   a. Polyuria, polydipsia, weight loss
   b. Signs of extreme dehydration and volume depletion—hypotension, tachycardia
   c. **CNS findings and focal neurologic signs are common** (e.g., seizures)—secondary to hyperosmolarity

d. Lethargy and confusion may develop, leading to convulsions and coma

3. **Diagnosis**
   a. Hyperglycemia: serum glucose typically **higher than DKA** and frequently >**600 mg/dL**
   b. Hyperosmolarity: serum osmolarity >320 mOsm/L
   c. Serum pH >7.3 (no acidosis); serum HCO_3^- >18
   d. BUN is usually elevated. Prerenal azotemia is common
4. **Treatment**
   a. **Fluid replacement** is most important (normal saline or lactated Ringer's): 1 L in the first hour, another liter in the next 2 hours. Most patients respond well. Switch to half normal saline or half LR once the patient stabilizes.
      - Glucose levels are lowered as the patient is rehydrated, but the patient still requires insulin. When glucose levels reach 300 mg/dL, add 5% dextrose (D5 1/2 NS or D5 1/2 LR). Note difference in goal from DKA.
      - Very rapid lowering of blood glucose can lead to cerebral edema in children (just as in DKA).
      - In patients with cardiac disease or renal insufficiency, avoid volume overload (can lead to CHF), but generous fluids are still needed.
   b. Insulin: Check to ensure serum K >3.3 prior to initiating. An initial bolus of 0.1 U/kg as IV bolus, followed by a continuous low-dose infusion (0.1 U/kg/hr) is usually appropriate.
   c. Monitor and replace potassium as needed to maintain K between 4 and 5 mEq/L. Ensure adequate renal function (urine output at least 50 mL/hr) before replacing K. Can add potassium to fluids as with DKA.

Quick HIT

Key Features of HHS

- Severe hyperosmolarity (>320 mOsm/L)
- Hyperglycemia (>600 mg/dL)
- Dehydration
- Acidosis and ketosis are absent (unlike in DKA)

Obesity

A. General Characteristics

1. BMI $\geq$30 kg/m^2
2. Over one-third of US population is obese (with an increasing prevalence in adolescents and children)
3. Obesity is associated with an increased risk of hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, NAFLD, obstructive sleep apnea, and osteoarthritis

B. Causes

1. Result of chronic mismatches in energy balance (energy intake > energy expenditure)
2. Energy balance determined by several variables, including **metabolic rate, appetite, diet, and physical activity**
3. These factors that determine energy balance are influenced by **both** genetic traits and environmental behaviors (such as excessive food intake, decreased physical activity).
4. Drug-induced (less common)—glucocorticoids, antipsychotics, antidepressants, oral hypoglycemics, and antiepileptics
5. Neuroendocrine disorders such as Cushing syndrome and polycystic ovarian syndrome (PCOS)

Quick HIT

BMI Classification:

- Underweight—BMI <18.5 kg/m^2
- Normal weight—BMI ≥18.5 kg/m^2 and <25 kg/m^2
- Overweight—BMI ≥25 kg/m^2 and <30 kg/m^2
- Obesity—BMI ≥30 kg/m^2
- Class I obesity—BMI ≥30 and <35 kg/m^2
- Class II obesity—BMI >35.0 to <40 kg/m^2
- Class III obesity—BMI ≥40 kg/m^2

C. Diagnosis

1. All adults should be screened by measuring height, weight, and calculating body mass index (BMI)
2. BMI = body weight (kg)/height^2 (meters)
3. Overweight and obese patients should be further screened with waist circumference to assess **abdominal obesity**
4. Waist circumference of ≥40 inches in men and ≥35 inches in women is considered elevated and corresponds with an increased **cardiometabolic risk**
5. Patients with abdominal obesity are at increased risk for heart disease, diabetes, hypertension, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD)

D. Treatment

1. The main treatment for obesity is **weight loss** through a combination of **diet, exercise**, and **behavioral modification.**
2. Medications if dieting and physical exercise are insufficient. For most patients, a GLP-1 agonist (e.g., semaglutide or liraglutide) is first-line therapy. Other options include **orlistat** (pancreatic lipase inhibitor) and combination **phentermine and topiramate** (sympathomimetic and appetite suppression).
3. **Bariatric surgery** remains the most effective treatment for obesity. It has been associated with long-term weight loss, improvement in obesity-related complications, and decreased mortality.
4. Indications for bariatric surgery include BMI ≥40 kg/m^2 who have not met weight loss goals with exercise and diet regimen or BMI >35 to

<40 kg/m^2 with at least one obesity-related comorbidity such as hypertension, diabetes mellitus, and hyperlipidemia.

Hypoglycemia

A. General Characteristics

1. **The primary organ at risk in hypoglycemia is the brain**—The brain uses glucose as its main energy source except when using ketone bodies during fasting (see also Clinical Pearl 4-5).
2. Unlike other tissues, the brain cannot use free fatty acids as an energy source.
3. Hypoglycemia is really due to an imbalance between glucagon and insulin.
4. If there is no correlation between the symptoms and low glucose levels (e.g., patient has symptoms when glucose levels are normal), an underlying disorder of glucose metabolism is unlikely (i.e., the patient does not have true hypoglycemia).

CLINICAL PEARL 4-5

Physiologic Responses to Hypoglycemia

- When glucose levels approach the low 80s, insulin levels decrease—This decrease is normally enough to prevent hypoglycemia.
- As glucose levels decrease further, glucagon levels increase. Glucagon is the first line of defense against more severe hypoglycemia.
- Epinephrine is the next hormone to combat hypoglycemia. Cortisol and other catecholamines also play a role.
- As glucose levels decrease into the 50s and below, symptoms begin.

B. Causes

1. Drug-induced—taking too much insulin is a common problem in diabetic patients attempting tight control of their disease. Other drugs such as sulfonylureas and meglitinides can also cause hypoglycemia
2. Factitious hypoglycemia

a. If the patient took insulin surreptitiously, there will be a high blood insulin level and a low blood C-peptide level because exogenous insulin does not contain C-peptide
b. If the patient took oral hypoglycemic agent such as sulfonylurea, check urine or serum for levels of this drug

3. Insulinoma
4. Ethanol ingestion—due to:
    a. Poor nutrition that leads to decreased glycogen (and loss of glycogenolysis).
    b. Metabolism of alcohol that lowers nicotinamide adenine dinucleotide levels and decreases gluconeogenesis
5. Postoperative complications after gastric surgery (due to rapid gastric emptying)
6. Reactive (idiopathic) hypoglycemia—symptoms occur 2 to 4 hours after a meal; rarely indicates a serious underlying disorder
7. Cortisol insufficiency
8. Liver failure
9. Critical illness
10. Malnourishment
11. Disorders of carbohydrate metabolism (e.g., glycogen storage diseases)—usually diagnosed at a much younger age

Quick HIT

If a patient presents with hypoglycemia of unknown cause, measure:
- Glucose
- Plasma insulin level
- C-peptide
- Proinsulin
- Beta-hydroxybutyrate
- Plasma and urine sulfonylurea levels

Quick HIT

Hypoglycemic Unawareness

- In diabetic patients, if severe neuropathy is present, the autonomic response to hypoglycemia is not activated. This leads to neuroglycopenic symptoms.
- It is common for diabetic patients to become hypoglycemic with conventional therapy (insulin or oral hypoglycemics). With longstanding disease in which they lose their neurogenic symptom response to hypoglycemia, patients do not recognize the impending hypoglycemia and may even have a seizure or enter a coma.

C. Clinical Features

1. Symptoms usually occur at a blood glucose level of 40 to 50 mg/dL.
2. Elevated catecholamine levels cause sweating, tremors, tachycardia, elevated BP, anxiety, and palpitations.
3. Neuroglycopenic symptoms—decreased glucose for the brain (CNS dysfunction), resulting in irritability, behavioral changes, dizziness, weakness, drowsiness, headache, confusion, convulsions, coma, and even death.

D. Diagnosis

1. Blood glucose level—Symptoms generally begin when levels drop below 50. However, there is no cutoff value to define hypoglycemia.
2. **Whipple triad** is used to diagnose true hypoglycemia (i.e., hypoglycemia due to underlying disease). (see the **Insulinoma** section.)
3. Laboratory tests—for measurement of serum insulin, C-peptide, proinsulin, beta-hydroxybutyrate, and glucose when symptoms occur. An overnight fast may be sufficient to produce symptoms.
4. 72-hour fast (24 hours is usually sufficient)—used to diagnose insulinoma if suspected.

E. Treatment

1. Acute treatment of hypoglycemia.
   a. If the patient can eat, give sugar-containing foods; if not, give 1/2 to 2 ampules of D50W intravenously.

   b. Repeat administration of D50W as necessary, but switch to D10W as clinical condition improves and glucose level is approximately >100 mg/dL.
2. Appropriate management of underlying cause (e.g., diabetes, insulinoma).
3. If reactive hypoglycemia is suspected, dietary interventions are appropriate.
4. If the patient has alcohol use disorder and hypoglycemia, treat hypoglycemia (do not delay treatment of life-threatening hypoglycemia to give thiamine). If thiamine deficiency is suspected, give thiamine supplementation as soon as able to prevent Wernicke encephalopathy.

Insulinoma

A. General Characteristics

1. Insulin-producing tumor arising from the β-cells of the pancreas
2. Associated with MEN I syndrome
3. Usually benign (in up to 90% of the cases)

B. Clinical Features

Hypoglycemia, which leads to:

1. Sympathetic activation—diaphoresis, palpitations, tremors, high blood pressure, anxiety
2. Neuroglycopenic symptoms—headache, visual disturbances, confusion, seizures, coma

C. Diagnosis

1. 72-hour fast (see also Table 4-7)
   a. The patient becomes hypoglycemic. Normally, the insulin level should decrease as hypoglycemia develops
   b. In persons with insulinoma, insulin does not respond appropriately to hypoglycemia. It may decrease or increase, or it may not change. Nevertheless, the insulin levels are still higher than they would be in a normal individual for any given glucose concentration

2. Whipple triad
    a. Hypoglycemic symptoms brought on by fasting
    b. Blood glucose <50 mg/dL during symptomatic attack
    c. Glucose administration brings relief of symptoms
3. Elevated fasting serum insulin level. C-peptide levels should also be elevated, which distinguishes insulinoma from exogenous insulin administration

D. Treatment

Surgical resection of tumor (up to 80% to 90% cure rate)

Zollinger–Ellison Syndrome (ZES, Gastrinoma)

- A duodenal or pancreatic neuroendocrine tumor that secretes high gastrin, which leads to profound gastric acid hypersecretion, resulting in ulcers.
- Up to 60% are malignant; 20% associated with MEN I (80% are sporadic); 90% located in the “gastrinoma triangle” (formed by the following points: cystic duct superiorly, junction of second and third portions of the duodenum inferiorly, and neck of pancreas medially).
- Possible complications: GI hemorrhage, GI perforation, gastric outlet obstruction/stricture, and metastatic disease (liver is the most common site).
- Clinical features: peptic ulcer disease, diarrhea, weight loss, abdominal pain.
- Secretin stimulation test is diagnostic test of choice. Normally, secretin inhibits gastrin secretion. In patients with ZES, gastrin levels increase substantially after being given secretin.
- Fasting gastrin level is elevated in patients with ZES.
- Treatment consists of proton pump inhibitors.
- All patients with ZES without metastates should undergo exploration to attempt curative resection (20% of patients are cured with complete resection). If there is widely metastatic or incurable gastrinoma, debulking surgery and chemotherapy are indicated.

TABLE 4-7 Laboratory Values in Hyperinsulinemic Hypoglycemia

	Laboratory Value			
Diagnosis	**Insulin Level**	**Glucose Level**	**C-Peptide Level**	**Proinsulin Level**
Insulinoma	↑	↓	↑	↑
Surreptitious insulin	↑↑	↓	↓	↓
Oral hypoglycemic agent	↑	↓	↑	Normal

Glucagonoma

- A neuroendocrine tumor that secretes glucagon, usually located in the pancreas.
- Clinical manifestations include **necrotizing migratory erythema** (usually below the waist), glossitis, stomatitis, DM (mild), and hyperglycemia (with low amino acid levels and high glucagon levels).
- Treatment is surgical resection.

Somatostatinoma

- A rare, usually malignant neuroendocrine tumor that secrete somatostatin (usually located in pancreas, duodenum, or jejunum); metastases usually are present by diagnosis.
- Poor prognosis
- Classic triad of gallstones, diabetes, and steatorrhea

VIPoma (Verner–Morrison or Watery Diarrhea, Hypokalemia, Achlorhydria Syndrome)

- A rare pancreatic neuroendocrine tumor (>50% are malignant).
- Clinical features include watery diarrhea (leading to dehydration, hypokalemia, acidosis), achlorhydria (VIP inhibits gastric acid secretion),

hyperglycemia, and hypercalcemia.
- Treatment is surgical resection.

Diseases of the Thyroid Gland

Hyperthyroidism

A. Causes

1. **Graves disease (diffuse toxic goiter)** is the most common cause—80% of all cases.
   a. An autoimmune disorder: A thyroid-stimulating immunoglobulin (IgG) antibody binds to the TSH receptors on the surface of thyroid cells and triggers the synthesis of excess thyroid hormone.
   b. Seen most often in younger women. Commonly associated with other autoimmune disorders.
   c. A radioiodide scan shows diffuse uptake because every thyroid cell is hyperfunctioning.
2. **Toxic multinodular goiter (Plummer disease)**—15% of all cases
   a. Characterized by hyperfunctioning areas that independently produce high T_4 and T_3 levels, thereby decreasing TSH levels. As a result, the rest of the thyroid is not functioning (atrophy due to decreased TSH).
   b. Consequently, *patchy uptake* appears on the thyroid scan.
   c. More common in elderly patients, and more common in women than men.

Quick HIT

Hyperthyroidism in the Elderly

- In the elderly, classic symptoms of hyperthyroidism (e.g., nervousness, insomnia, hyperactivity) may be absent. The only manifestations may be weight loss, weakness, and/or atrial fibrillation.
- Consider hyperthyroidism before assuming that an elderly patient with unexplained weight loss has depression or occult malignancy.

3. Toxic thyroid adenoma (single nodule)—2% of all cases.
4. Hashimoto thyroiditis and subacute (granulomatous) thyroiditis (both can cause **transient** hyperthyroidism).
5. Other causes (rare)
   a. Postpartum thyroiditis (transient hyperthyroidism)
   b. Iodine-induced hyperthyroidism (iodine load leads to transient hyperthyroidism)
   c. Excessive doses of levothyroxine (e.g., iatrogenic by health care provider or surreptitious self-administration)

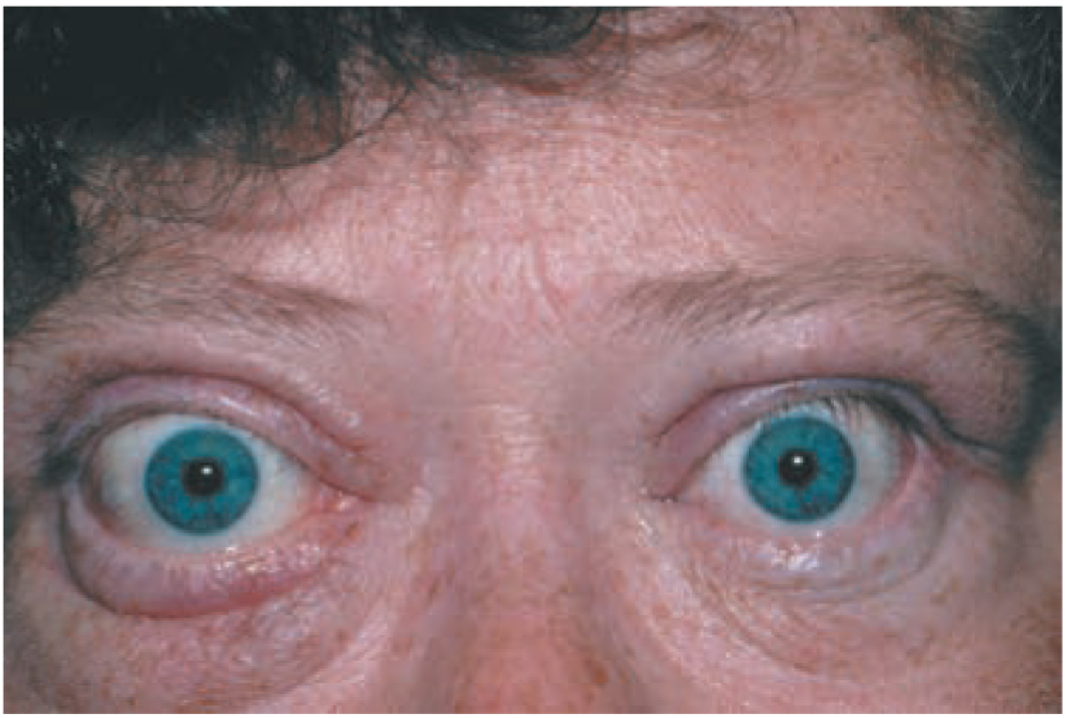


FIGURE 4-6 **Exophthalmos (thyrotoxicosis).** (Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Photo 25.9.)

B. Clinical Features

1. Symptoms
   a. Nervousness, insomnia, irritability
   b. Hand tremor, hyperactivity, tremulousness
   c. Excessive sweating, heat intolerance

d. Weight loss despite increased appetite
e. Diarrhea
f. Palpitations (due to tachyarrhythmias)
g. Muscle weakness

Quick HIT

There are three signs of hyperthyroidism specific to Graves disease:

- Exophthalmos
- Pretibial myxedema
- Thyroid bruit

2. Signs
   a. Thyroid gland
      - Graves disease: a diffusely enlarged (symmetric), nontender thyroid gland; **a bruit may be present.**
      - Subacute thyroiditis: an exquisitely tender, diffusely enlarged gland (with a viral illness).
      - Toxic multinodular goiter and Hashimoto thyroiditis (if multinodularity is present): thyroid gland is bumpy, irregular, and asymmetric.
      - Toxic adenoma: single nodule with an otherwise atrophic gland.
   b. Extrathyroidal
      - Eyes: **Proptosis, due to edema of the extraocular muscles and retro-orbital tissue, is a hallmark of Graves disease** (but not always present). Irritation and excessive tearing are common due to corneal exposure. Lid retraction may be the only sign in milder disease (Figure 4-6). Lid lag may be present.
      - Cardiovascular effects: arrhythmias (sinus tachycardia, atrial fibrillation, and premature ventricular contractions), elevated BP.
      - Skin changes: warm and moist, **pretibial myxedema** (edema over tibial surface due to dermal accumulation of mucopolysaccharides).
      - Neurologic: brisk deep tendon reflexes, tremor.

C. Diagnosis

1. Serum TSH level (low)—**initial test of choice:** If TSH is normal or high, hyperthyroidism is unlikely. (TSH-induced hyperthyroidism is quite uncommon.)
2. Next order thyroid hormone levels: T_4 level should be elevated.
3. Testing the T_3 level is usually unnecessary but may be helpful if TSH level is low and free T_4 is not elevated, because excess T_3 alone can cause hyperthyroidism.
4. Radioactive iodine uptake scan. High uptake indicates de novo synthesis of thyroid hormone (Graves disease, toxic multinodular goiter, toxic adenoma). Low uptake indicates inflammation or destruction of thyroid tissue leading to release of thyroid hormone, or extrathyroidal thyroidal hormone (subacute thyroiditis, factitious thyrotoxicosis).
5. Thyrotropin receptor antibodies will be positive in Graves disease.
   a. Free thyroxine index (FTI).
      - FTI is proportional to actual free T_4 concentration; it is calculated to correct for changes in thyroid-binding proteins.
      - FTI = (radioactive T_3 uptake x serum total T_4)/100.
      - FTI = (patient's radioactive T_3 uptake/normal radioactive T_3 uptake) × total T_4.
      - Normal FTI values are 4 to 11. FTI should not change (as T_4 decreases, radioactive T_3 uptake increases and vice versa).
      - Infrequently ordered due to newer methods of measuring free T_4 directly.

Quick HIT

Thyroid Hormones and TBG

- T_4 is converted to T_3 by deiodination outside of the thyroid.
- T_3 is more biologically active than T_4.
- Most of T_4 (and T_3) is reversibly bound to thyroxine-binding globulin (TBG) and is inactive.
- Factors that increase TBG (and therefore total T_4) include pregnancy, liver disease, and estrogen therapy.

D. Treatment Types

1. Pharmacologic
   a. Thionamides—Methimazole and propylthiouracil (PTU) inhibit thyroid hormone synthesis, and PTU also inhibits conversion of T_4 to T_3. Methimazole is usually the drug of choice as it is more rapidly effective and has fewer side effects. Treatment with thionamides results in long-term remission in a minority of patients; a major serious side effect is agranulocytosis. Other side effects shared by both methimazole and PTU include skin rash, arthralgias, and hepatotoxicity.
   b. β-Blockers—for acute management of some symptoms such as palpitations, tremors, anxiety, tachycardia, sweating, and muscle weakness.
   c. Sodium ipodate or iopanoic acid—lowers serum T_3 and T_4 levels and causes rapid improvement of hyperthyroidism; appropriate for acute management of severe hyperthyroidism that is not responding to conventional therapy.
2. Radioiodine 131 (^{131}I)
   a. Causes destruction of thyroid follicular cells.
   b. Most common therapy in the United States for Graves disease.
   c. Main complication is hypothyroidism and occurs in majority of patients.
   d. If the first dose does not control the hyperthyroidism within 6 to 12 months, then administer another dose.

e. Contraindicated during pregnancy and breastfeeding due to risk of cretinism (stunted physical and mental growth from severe hypothyroidism).

3. Surgical—subtotal thyroidectomy
   a. Very effective, but only 1% of patients with hyperthyroidism are treated with surgery due to the following side effects: permanent hypothyroidism (30%), recurrence of hyperthyroidism (10%), recurrent laryngeal nerve palsy (1%), and permanent hypoparathyroidism (1%).
   b. Often reserved for patients with very large goiters (more common in toxic multinodular goiter), those who are allergic to antithyroid drugs, or patients who prefer surgery over medication.
   c. Watch for clinical manifestations of hypocalcemia after surgery that may not return to normal due to parathyroid inflammation or accidental removal.

Quick HIT

For all patients taking antithyroid medication, consider monitoring the leukocyte count for agranulocytosis on a regular basis.

Quick HIT

Thyroid cells are the only cells in the body that absorb iodine. Therefore, giving radioactive iodine destroys only thyroid cells.

E. Treatment

1. For immediate control of adrenergic symptoms of hyperthyroidism (of any cause): β-blocker (propranolol)
2. For *nonpregnant* patients with Graves disease
   a. Start methimazole (in addition to the β-blocker)
   b. Taper β-blocker after 4 to 8 weeks (once methimazole starts to take effect)
   c. Continue methimazole for 1 to 2 years. Measure thyroid-stimulating IgG antibody at 12 months. If high levels of antibodies are present,

high risk for relapse and should continue methimazole or switch to definitive therapy (radioiodine therapy or surgery)

3. For *pregnant* patients with Graves disease
   a. Endocrinology consult is indicated before starting treatment
   b. **PTU is preferred**
4. Radioactive iodine ablation therapy
   a. Leads to hypothyroidism over time in many patients
   b. Consider therapy with ^{131}I for the following patients:
      - Elderly patients with Graves disease
      - Patients with a solitary toxic nodule
      - Patients with Graves disease in whom therapy with antithyroid drugs fails (e.g., due to relapse, agranulocytosis)

A 32-year-old woman with a history of endometriosis presents with weight loss, diarrhea, and increased appetite for the past 6 weeks. She has a temperature of 37°C, blood pressure of 132/88 mmHg, heart rate of 75 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 99% on room air. Physical examination reveals a diffusely large, nontender thyroid gland. Laboratory studies confirm the diagnosis and the patient opts for treatment with methimazole.

Which of the following adverse effects is important to inform the patient of before beginning treatment with this medication?

A. Hypocalcemia
B. Acute liver failure
C. Agranulocytosis
D. Vasculitis

- **The answer is C: Agranulocytosis.** The patient in this question likely has Graves disease. There are several side effects of propylthiouracil and methimazole, several of which are shared by both drugs and some that are unique to each one. Side effects that are shared by both include skin rash, arthralgias, hepatotoxicity, and agranulocytosis. Methimazole can cause jaundice and is teratogenic in the first trimester. **(B, D)** Propylthiouracil (PTU) can cause vasculitis and carries a risk of acute liver failure. **(A)** Hypocalcemia is indeed an adverse effect from thyroidectomy, but the patient in this question opted for medical management over surgery.

Thyroid Storm

- **This is a rare, life-threatening complication of thyrotoxicosis** characterized by an acute exacerbation of the manifestations of hyperthyroidism.

- There is usually a precipitating factor, such as infection, DKA, large iodine load, or stress (e.g., severe trauma, surgery, illness, childbirth).
- **High mortality rate: up to 10% to 30%.**
- Clinical manifestations include marked fever, tachycardia, agitation or psychosis, confusion, and GI symptoms (e.g., nausea, vomiting, diarrhea).
- Provide supportive therapy with IV fluids, cooling blankets, and glucose.
- Give antithyroid agents (PTU or methimazole every 4 to 6 hours). PTU is favored because of its ability to decrease T_4 to T_3 conversion. Follow with iodine to inhibit thyroid hormone release.
- Administer β-blockers for control of heart rate. Give glucocorticoids (e.g., hydrocortisone) to impair T_4 to T_3 conversion and to provide adrenal support.

Quick HIT

The terms hyperthyroidism and thyrotoxicosis are interchangeable and refer to hyperfunctioning thyroid disease. **Thyroid storm is a medical emergency with life-threatening sequelae.**

Hypothyroidism

A. General Characteristics

1. The onset of symptoms is usually insidious, and the condition may go undetected for years (see also Clinical Pearl 4-6).
2. Sometimes a diagnosis is made solely on laboratory evidence in an asymptomatic patient.

CLINICAL PEARL 4-6

Myxedema Coma

- A rare condition that presents with a depressed state of consciousness, profound hypothermia, and respiratory depression.
- May develop after years of severe untreated hypothyroidism.
- Precipitating factors are trauma, infection, cold exposure, and opioids.
- **A medical emergency, with a high mortality rate (30% to 50%) even with treatment.**
- Provide supportive therapy to maintain BP and respiration. Give IV thyroxine and glucocorticoids (hydrocortisone) while carefully monitoring the hemodynamic state.

B. Causes

1. Primary hypothyroidism is the failure of the thyroid to produce sufficient thyroid hormone. This accounts for about 95% of all cases
   a. **Hashimoto disease (chronic autoimmune thyroiditis)**—most common cause of primary hypothyroidism in iodine-sufficient parts of the world
   b. Iodine deficiency is the most common cause of hypothyroidism worldwide
   c. Iatrogenic—second most common cause of primary hypothyroidism; results from prior treatments of hyperthyroidism, including:
      - Radioiodine therapy
      - Thyroidectomy
      - Radiation to neck
      - Medications (e.g., lithium, amiodarone, checkpoint inhibitor immunotherapy, and oral tyrosine kinase inhibitors)
2. Secondary hypothyroidism (due to pituitary disease; i.e., deficiency of TSH) and tertiary hypothyroidism (due to hypothalamic disease; i.e., deficiency of TRH) account for less than 1% of cases. **Both are associated with a low free T_4 and a low TSH level**

Quick HIT

Hashimoto thyroiditis is associated with other autoimmune disorders (e.g., systemic lupus erythematosus, pernicious anemia).

Patients with Hashimoto thyroiditis are at an increased risk of thyroid cancer.

C. Clinical Features

1. Symptoms
   a. Fatigue, weakness, lethargy
   b. Heavy menstrual periods (menorrhagia)
   c. Slight weight gain—patients are **not** typically obese
   d. Cold intolerance
   e. Constipation
   f. Slow mentation, inability to concentrate (mild at first, in later stages dementia can occur), dull expression
   g. Muscle weakness, arthralgias
   h. Depression
   i. Diminished hearing
2. Signs
   a. Dry skin, coarse hair; thickened, puffy features
   b. Enlargement of the tongue and hoarseness
   c. Nonpitting edema (edema due to glycosaminoglycan in interstitial tissues)
   d. Carpal tunnel syndrome
   e. Delayed relaxation of deep tendon reflexes
   f. Loss of lateral portion of eyebrows
   g. Bradycardia
   h. Goiter (Hashimoto disease—goiter is rubbery, nontender, and even nodular; subacute thyroiditis—goiter is very tender and enlarged, although not always symmetrically)
   i. History of upper respiratory infection and fever (subacute thyroiditis)

D. Diagnosis

1. **High TSH level—most sensitive indicator of hypothyroidism** (see also Clinical Pearl 4-7).
2. Low TSH level in secondary or tertiary hypothyroidism.
3. Low free T_4 level (or free T_4 index) in patients with clinically overt hypothyroidism. Free T_4 may be normal in subclinical cases.
4. **Increased thyroid peroxidase (TPO) antibodies (Hashimoto thyroiditis).**
5. Other laboratory value abnormalities that may be present:
   a. Elevated LDL and decreased HDL levels
   b. Anemia—mild normocytic, hypoproliferative anemia is the most common

CLINICAL PEARL 4-7

Subclinical Hypothyroidism

- Thyroid function is inadequate, but increased TSH production maintains T_4 level within the reference range of normalcy; therefore, TSH level is elevated and T_4 level is normal.
- Look for nonspecific or mild symptoms of hypothyroidism, as well as elevated serum LDL levels.
- Treat with thyroxine if patients develop goiter, hypercholesterolemia, symptoms of hypothyroidism, significantly elevated TSH level (>10 μU/mL), or patients attempting pregnancy.

Quick HIT

TSH is the primary test in screening for thyroid dysfunction. Also order a free T_4 level, lipid profile, and a CBC.

E. Treatment

Levothyroxine (T_4)—treatment of choice

1. Effect is evident in 2 to 4 weeks; highly effective in achieving euthyroid state
2. Convenient once—daily morning dose
3. Treatment is continued indefinitely
4. Monitor TSH level and clinical state periodically

Thyroiditis

A. Subacute Thyroiditis (subacute granulomatous thyroiditis, de Quervain thyroiditis)

1. Causes—usually follows a viral illness; associated with HLA-B35
2. Clinical features
   a. Prodromal phase that lasts a few weeks (fever, flu-like illness)
   b. It can cause transient hyperthyroidism due to leakage of hormone from inflamed thyroid gland. This is followed by a euthyroid state and then a hypothyroid state (as hormones are depleted)
   c. **Painful,** tender thyroid gland (may be enlarged)
3. Diagnosis
   a. **Radioiodine uptake is low** because thyroid follicular cells are damaged and cannot trap iodine
   b. Low TSH level secondary to suppression by increased T_4 and T_3 levels; high inflammatory markers (erythrocyte sedimentation rate or C-reactive protein)
4. Treatment
   a. Use NSAIDs and aspirin for mild symptoms; corticosteroids, if the pain is more severe
   b. Most patients have recovery of thyroid function within a few months to 1 year

B. Subacute Lymphocytic Thyroiditis (painless thyroiditis, silent thyroiditis)

1. A transient thyrotoxic phase of 2 to 5 months may be followed by a hypothyroid phase. The hypothyroid phase is usually self-limited and may be the only manifestation of this disease if the hyperthyroid phase is brief.

2. Low radioactive iodine uptake—differentiates it from Graves disease during thyrotoxic phase.
3. Similar to subacute (viral) thyroiditis, only *without the pain or tenderness* of the thyroid gland.

C. Hashimoto Thyroiditis (chronic lymphocytic thyroiditis, chronic autoimmune thyroiditis)

1. Most common cause of autoimmune thyroid disorder; more common in women.
2. Causes
   a. Genetic component—family history is common.
   b. Antithyroid antibodies are present in the majority of patients.
3. Clinical manifestations (see also Clinical Pearl 4-8)
   a. Goiter is the most common feature.
   b. Slow decline in thyroid function is common. Hypothyroidism is present in 20% of cases when first diagnosed but often occurs later in disease.
4. Diagnosis
   a. Thyroid function studies are normal (unless hypothyroidism is present).
   b. Antithyroid antibodies: antithyroid peroxidase antibodies (present in 90% of patients), antithyroglobulin antibodies (present in 50%).
   c. Irregular distribution of ^{131}I on thyroid scan—not required for diagnosis.
5. Treatment—thyroid hormone (to achieve euthyroid state)

CLINICAL PEARL 4-8

Thyroid-Associated Ophthalmopathy (TAO)

- TAO is an autoimmune attack on the periorbital connective tissue and extraocular muscles.
- Clinical findings include lid retraction ("thyroid stare"), proptosis, eyelid edema, lagophthalmos (inability to close eyelids completely), and diplopia.
- Patients may be hypothyroid, hyperthyroid (Graves disease), or euthyroid when TAO presents. Most euthyroid patients will go on to develop thyroid dysfunction within 2 years of developing TAO.
- Treatment of thyroid dysfunction has little effect on the course of TAO. TAO is usually self-limited, but surgery may be required if disease is severe. Oral steroids may also be helpful.

D. Fibrous Thyroiditis (Riedel thyroiditis, invasive thyroiditis)

1. Fibrous tissue replaces thyroid tissue, leading to a firm thyroid.
2. Surgery may be necessary if complications occur.
3. Patient may be hypothyroid as well, in which case thyroid hormone should be prescribed.

Thyroid Nodules

A. General Characteristics

1. Cancer is found in 5% to 10% of nodules that are investigated.
2. A solitary nodule can be either thyroid cancer or a benign adenoma. However, multinodular conditions may cause confusion because only one of these nodules may be palpable.
3. The most important function of the physical examination is the detection of the thyroid nodule, rather than the determination of its benign or malignant status.
4. To be detectable on palpation, a nodule must be at least 1 cm in diameter.
5. Malignancy is suggested by the following:
   a. Fixed nodule that does not move with swallowing

b. Unusually firm consistency or irregularity of the nodule
c. Solitary nodule
d. History of radiation therapy to the neck
e. History of rapid development
f. Vocal cord paralysis (recurrent laryngeal nerve paralysis)
g. Cervical lymphadenopathy
h. Family history of thyroid cancer

B. Diagnosis

1. Initial workup should include history, physical examination, ultrasound of neck and TSH.
2. Fine-needle aspiration (FNA) biopsy (see also Clinical Pearl 4-9)
   a. FNA has a sensitivity of 95% and a specificity of 95%. Therefore, if FNA shows a benign nodule, the nodule is likely to be benign.
   b. However, FNA biopsies have 5% false-negative results, so follow up with periodic FNA if thyroid nodularity persists. Benign lesions should continue to show consistently benign cytology.
   c. FNA is reliable for all cancers (papillary, medullary, anaplastic) **except follicular.**

CLINICAL PEARL 4-9

Fine-Needle Aspiration

- Patient should first be evaluated with ultrasound and TSH level.
- A needle is inserted into the nodule, and cells are aspirated and then examined under a microscope.
- False-positive and false-negative rates approach 5%.
- **This is the only test that can reliably differentiate between benign and malignant nodules.**
  - Ultrasound differentiates between solid and cystic nodules, but either may be malignant.
  - On the thyroid scan, “cold” nodules are more likely to be malignant than “hot,” but this is not reliable.
- FNA findings:
  - Suspicious for malignancy or malignant: Surgery is indicated.
  - Indeterminate: A thyroid scan should be performed, and if the lesion is “cold” by the scan, surgical resection is indicated because about 20% of these lesions are found to be malignant.
  - Benign: Most are benign. Observe with periodic ultrasound (usually at 1 year).
  - Follicular neoplasm: Surgery is recommended because it is difficult to distinguish between benign and malignant follicular cells on histology.
  - Nondiagnostic. Repeat FNA in 4 to 6 weeks.

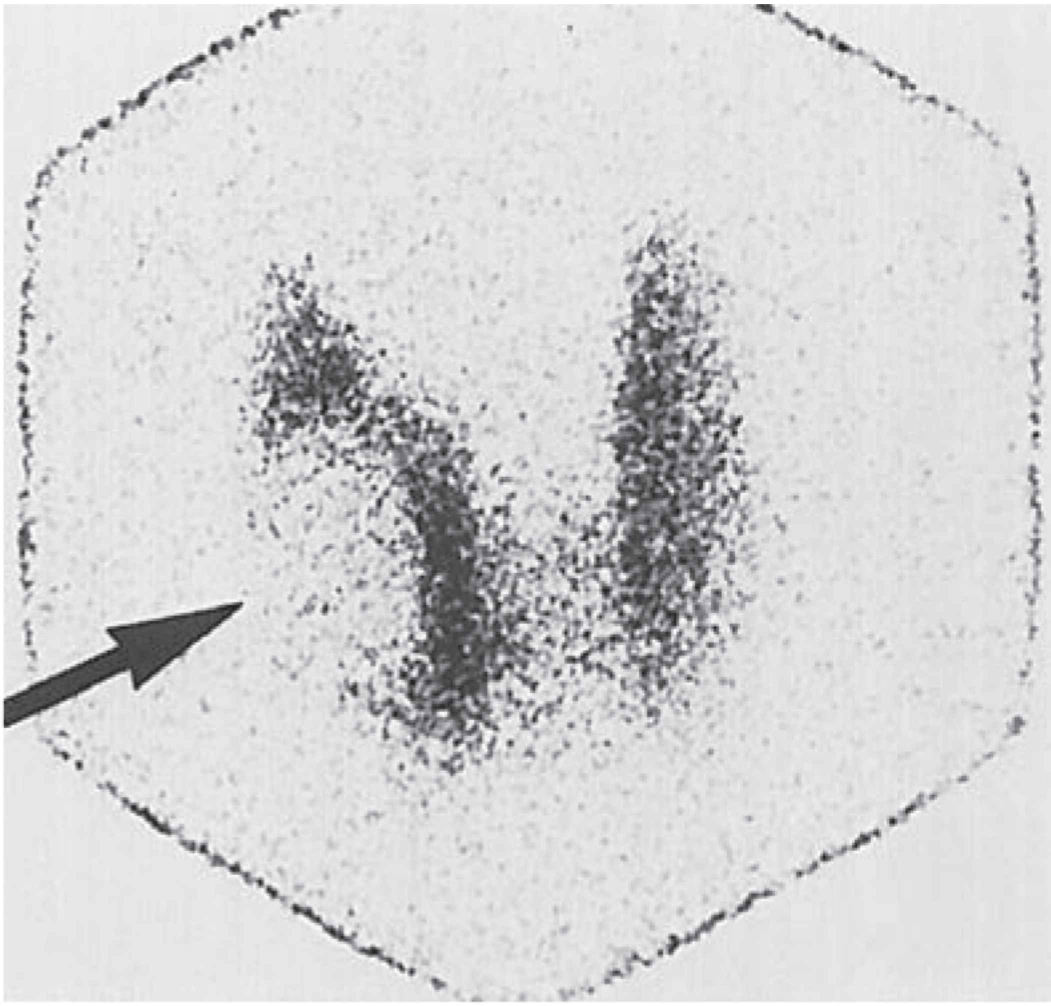


FIGURE 4-7 **A ^{123}I thyroid scan showing a large "cold" nodule (*arrow*).**
(Reprinted with permission from Fishman MC, Hoffman AR, Klausner RD, et al. *Medicine*. 5th ed. Lippincott Williams & Wilkins; 2004:185. Figure 22-1.)

3. Thyroid scan (radioactive iodine) (Figure 4-7)
   a. Thyroid scan plays a supplemental role. It is performed if the FNA biopsy is indeterminate. It is also performed in patients with a low TSH, as these patients are more likely to have a hyperfunctioning nodule.
   b. It gives graphic representations of the distribution of radioactive iodine in the gland—useful in identifying whether thyroid nodules show decreased ("cold") or increased ("hot") accumulation of radioactive iodine compared with normal paranodular tissue.

Nodules are classified as “cold” (hypofunctional), “hot” (hyperfunctional), or indeterminate (usually nonfunctioning).

c. Due to cost, it should be limited to patients whose FNA biopsy results suggest neoplasm or for those with suppressed TSH (as a hyperfunctioning nodule has low risk of malignancy so does not require FNA). When such lesions are “cold” on scan, thyroid lobectomy is recommended.

4. Thyroid ultrasound
   a. Differentiates a solid from a cystic nodule; most cancers are solid.
   b. Can identify nodules 1 to 3 mm in diameter.
   c. Cystic masses larger than 4 cm in diameter are not malignant.
   d. Cannot distinguish between benign and malignant thyroid nodules.

Quick HIT

In general, most patients with thyroid cancer do not die of thyroid cancer (although this depends on the type of thyroid cancer; anaplastic and follicular thyroid cancer have higher mortality).

Thyroid Cancer

A. General Characteristics

1. Risk factors
   a. Head and neck radiation (during childhood)
   b. Family history: Gardner syndrome and Cowden syndrome for papillary cancer**, MEN type II** for medullary cancer

CLINICAL PEARL 4-10

Nodules

"Cold" Nodules

- Decreased iodine uptake = hypofunctioning nodule.
- Significant risk of malignancy—approximately 5% of cold nodules are malignant.
- Of all nodules, 70% to 90% are cold and most of these are benign. Therefore, scanning may indicate a greatly reduced risk of malignancy in a nodule that is warm or hot, but it does not yield much additional information in a nodule that is cold.

"Hot" Nodules

- Increased iodine uptake = hyperfunctioning nodule.
- Rarely associated with malignancy.

2. Types (see also Clinical Pearl 4-10)
   a. Papillary carcinoma
      - Accounts for more than 80% of all thyroid cancers
      - Least aggressive thyroid cancer—slow growth and slow spreading with excellent prognosis
      - Most important risk factor is a history of radiation to the head/neck
      - Spreads via lymphatics in neck; frequently metastasizes to cervical lymph nodes (cervical lymphadenopathy); distant metastasis is rare
      - Positive iodine uptake
   b. Follicular carcinoma
      - Accounts for 15% of all thyroid cancers; avidly absorbs iodine.
      - Prognosis is worse than for papillary cancer—it spreads early via a hematogenous route (brain, lung, bone, liver). Distant metastasis occurs in 15% of patients; lymph node involvement is uncommon.
      - May be associated with iodine deficiency, as prevalence is higher in iodine-deficient areas of the world.
      - Tumor extension through the tumor capsule or vascular invasion distinguishes it from a benign adenoma. A tissue sample is therefore needed for diagnosis.

- More malignant than papillary cancer, but these are also slow growing.
- Hürthle cell cancer was previously thought to be a variant (now a distinct tumor type similar to follicular cancer)—characteristic cells contain abundant cytoplasm, tightly packed mitochondria, and oval nuclei with prominent nucleoli. These tumors are radioiodine resistant.

c. Medullary carcinoma

- Accounts for 1%to 2% of all thyroid cancers in the United States.
- Most are sporadic, 25% are familial and associated with MEN II (always screen for pheochromocytoma).
- Arises from the parafollicular cells (C cells)—**produces calcitonin and CEA.**
- Mortality is worse than papillary and follicular cancer, but less than anaplastic cancer. 10-year survival rate is 70% to 80%.

d. Anaplastic carcinoma

- Accounts for 5% of all thyroid cancers; mostly seen in elderly patients.
- Highly aggressive with rapid disease progression.
- May arise from a longstanding follicular or papillary thyroid carcinoma.
- Prognosis (grim)—death typically occurs within a few months. Mortality is usually due to invasion of adjacent organs (trachea, neck vessels).

***Quick* HIT**

Hürthle Cell Tumor

- A distinct tumor type similar to follicular thyroid cancer
- Spread by lymphatics; does not take up iodine.
- Treatment: total thyroidectomy.

Quick HIT

Papillary carcinoma is the most common type of thyroid cancer to develop after radiation exposure (accounts for 80% to 90% of postradiation cancers of the thyroid).

B. Diagnosis

1. Thyroid hormone level (frequently normal)
2. Calcitonin and CEA level (if medullary carcinoma)
3. Refer to the section on thyroid nodules for diagnostic approach

C. Treatment

1. Papillary carcinoma
   a. Lobectomy with isthmusectomy
   b. Total thyroidectomy if tumor is >4 cm, tumor is bilateral, tumor is advanced, or distant metastases are present
   c. Adjuvant treatment: TSH suppression therapy; radioiodine therapy for larger or higher-risk tumors
2. Follicular carcinoma—similar treatment as papillary carcinoma
3. Medullary carcinoma—total thyroidectomy; radioiodine therapy not indicated as cells do not concentrate iodine. Modified radical neck dissection is also indicated when there is lymph node involvement (most cases)
4. Anaplastic carcinoma—chemotherapy and radiation may provide a modest improvement in survival. Palliative surgery for airway compromise may be needed

Diseases of the Pituitary Gland

Pituitary Adenomas

A. General Characteristics

1. Pituitary adenomas account for about 10% of all intracranial neoplasms.
2. Almost all pituitary tumors are benign. They may grow in any direction causing "parasellar" signs and symptoms.
3. Size: microadenoma (diameter ≤10 mm); macroadenoma (diameter >10 mm).

B. Clinical Features

1. Hormonal effects occur due to hypersecretion of one or more of the following hormones:
   a. Prolactin—see the following section on hyperprolactinemia
   b. Growth hormone (GH)—results in acromegaly (or gigantism if epiphyseal closure has not occurred; seen in the pediatric population)
   c. Adrenocorticotropic hormone (ACTH)—results in Cushing disease, many are clinically silent
   d. TSH—results in hyperthyroidism
2. Hypopituitarism—compression of hypothalamic–pituitary stalk; GH deficiency and hypogonadotropic hypogonadism are the most common problems
3. Mass effects
   a. Headache
   b. Visual defects—Bitemporal hemianopsia (due to compression of optic chiasm) is the most common finding, but it depends on the size and symmetry of the tumor

C. Diagnosis

1. **MRI** is the imaging study of choice
2. Pituitary hormone levels

D. Treatment

1. Transsphenoidal surgery is indicated in most patients (except patients with prolactinomas, for which medical management can be tried first).
2. Radiation therapy and medical therapy are adjuncts in most patients.

Hyperprolactinemia

A. Causes

1. Prolactinoma
   a. Most common cause of hyperprolactinemia
   b. Most common type of pituitary adenoma (up to 40%)
2. Medications (e.g., antipsychotics, antidepressants, metoclopramide, verapamil, estrogen)
3. Pregnancy
4. Renal failure
5. Suprasellar mass lesions (can compress hypothalamus or pituitary stalk)
6. Hypothyroidism
7. Idiopathic

Quick HIT

High levels of prolactin inhibit secretion of GnRH. This leads to decreased secretion of LH and FSH, which in turn leads to decreased production of estrogen and testosterone (see **Clinical Features**).

B. Clinical Features

1. Men
   a. Hypogonadism, decreased libido, infertility, erectile dysfunction
   b. Galactorrhea or gynecomastia (uncommon)
   c. Parasellar signs and symptoms (visual field defects and headaches)
2. Women
   a. Premenopausal: menstrual irregularities, oligomenorrhea or amenorrhea, anovulation and infertility, decreased libido,

dyspareunia, vaginal dryness, decreased bone density and osteoporosis, galactorrhea
b. Postmenopausal: parasellar signs and symptoms (less common than in men)

Quick HIT

Parasellar signs and symptoms (mass effects of the tumor) are more prevalent in men than in women. This is largely because the early symptoms in men (e.g., erectile dysfunction) are often attributed to other causes and medical evaluation is delayed, allowing for larger tumor growth.

C. Diagnosis

1. Elevated serum prolactin level.
2. Order a pregnancy test and TSH level, because both pregnancy and primary hypothyroidism are on the differential diagnosis for hyperprolactinemia.
3. CT scan or MRI to identify any mass lesions.

D. Treatment

1. Treat the underlying cause (e.g., stop medication, treat hypothyroidism).
2. If prolactinoma is the cause and the patient is symptomatic, treat with **cabergoline** or **bromocriptine,** both dopamine agonists that secondarily diminish the production and release of prolactin. Cabergoline is often better tolerated than bromocriptine and is often chosen as first-line therapy. Continue treatment for approximately 2 years before attempting cessation.
3. Consider surgical intervention if symptoms progress despite appropriate medical therapy. However, the recurrence rate after surgery is high.

Quick HIT

Microadenomas (<10 mm diameter) tend to either remain the same size or regress with time. Only 10% to 20% continue to grow.

Acromegaly

A. General Characteristics

1. Acromegaly is broadening of the skeleton, which results from excess secretion of pituitary GH after epiphyseal closure (if before epiphyseal closure, gigantism [excessive height] results).
2. It is almost always caused by a GH-secreting pituitary adenoma (represents one-third of pituitary adenomas).

Quick HIT

Cardiovascular disease (cardiomyopathy) is the most common cause of death in patients with acromegaly.

B. Clinical Features

1. Growth promotion
   a. Soft tissue and skeleton overgrowth
   b. Hyperhidrosis
   c. Coarsening of facial features
   d. Abnormally large hand and foot size (ask about increasing glove/ring size)
   e. Organomegaly
   f. Arthralgia due to joint tissue overgrowth
   g. Left ventricular hypertrophy, cardiomyopathy
   h. Enlarged jaw (macrognathia) and enlarged tongue (macroglossia)
   i. Obstructive sleep apnea
2. Metabolic disturbances
   a. Glucose intolerance and DM in 10% to 15% of patients
   b. Hyperphosphatemia
3. Parasellar manifestations
   a. Headache
   b. Superior growth leads to compression of the optic chiasm, which results in visual loss (**bitemporal hemianopsia**)
   c. Lateral growth leads to cavernous sinus compression
   d. Inferior growth leads to sphenoid sinus invasion

C. Diagnosis

1. Insulin-like growth factor (IGF-1), also known as somatomedin C, should be significantly elevated in acromegaly
2. Oral glucose tolerance test—glucose load fails to suppress GH (as it should in healthy individuals). This confirms the diagnosis if the IGF-1 level is equivocal
3. MRI of the pituitary
4. A random GH level is not useful because there is wide physiologic fluctuation of GH levels

Quick HIT

Other Laboratory Abnormalities in Patients With Acromegaly

- Hyperprolactinemia (tumor secretes prolactin and growth hormone)—30% of patients
- Elevations in serum glucose, triglycerides, and phosphate levels

D. Treatment

1. Transsphenoidal resection of pituitary adenoma—treatment of choice
2. Octreotide or other somatostatin analog to suppress GH secretion
3. Radiation therapy if medical therapy is unsuccessful after surgery

Craniopharyngioma

- Tumors of the suprasellar region arising from embryologic remnants of Rathke pouch.
- These tumors comprise 1% to 3% of all brain tumors.
- They result in visual field defects (bitemporal hemianopsia) due to compression of the optic chiasm and may also cause headaches, papilledema, and changes in mentation.
- They are diagnosed by brain MRI or CT.
- They may cause hyperprolactinemia, diabetes insipidus, or panhypopituitarism.
- Treatment is surgical excision (total or partial resection) with or without radiation therapy.

Quick HIT

Calcification of the suprasellar region seen on brain imaging is nearly diagnostic of craniopharyngioma.

Hypopituitarism

A. General Characteristics

1. All or some of the hormones released from the anterior pituitary may be absent.
2. Loss of hormones is unpredictable, but LH, FSH, and GH are usually lost before TSH and ACTH.
3. Clinical manifestations depend on which hormones are lost.

B. Causes

1. Hypothalamic or pituitary tumor is the most common cause.
2. Other causes: radiation therapy, infection, traumatic brain injury, pituitary infarct (Sheehan syndrome), pituitary apoplexy, infiltrative processes (e.g., sarcoidosis, hemochromatosis), cavernous sinus thrombosis, surgery.

C. Clinical Features

1. Reduced GH: growth failure (decreased muscle mass in adults), increased LDL, increased risk of heart disease, increased LDL
2. Reduced prolactin: failure to lactate
3. Reduced ACTH: adrenal insufficiency
4. Reduced TSH: hypothyroidism
5. Reduced gonadotropins (LH and FSH): infertility, amenorrhea, loss of secondary sex characteristics, diminished libido
6. Reduced antidiuretic hormone (ADH) (if hypothalamic lesion): diabetes insipidus
7. Reduced melanocyte-stimulating hormone (MSH): decreased skin and hair pigmentation

D. Diagnosis

1. Low levels of target hormones with low or normal levels of trophic hormones (it is the suppression of the trophic hormone that is important, although the absolute level may be in the normal reference range)
2. MRI of the brain (may miss microadenomas)

E. Treatment

1. Replacement of appropriate hormones
2. Patients who want to conceive should be referred to an endocrinologist

Diabetes Insipidus

A. General Characteristics

1. Two forms
   a. Central DI is the most common form—due to low ADH secretion by posterior pituitary.
   b. Nephrogenic DI—ADH secretion is normal but tubules cannot respond to ADH.

Quick HIT

If a patient presents with polyuria and polydipsia, consider the following in the differential diagnosis:
- Diabetes mellitus
- Diuretic use
- Diabetes insipidus
- Primary polydipsia

2. Causes
   a. Central DI
      - Idiopathic—50% of all cases
      - Trauma—surgery, head trauma
      - Other destructive processes involving the hypothalamus, including tumors, sarcoidosis, tuberculosis, syphilis, Langerhans cell histiocytosis, and encephalitis

b. Nephrogenic DI—the most common cause in adults is *chronic lithium use.* Other causes include hypercalcemia, kidney disease, and demeclocycline use. It may also be congenital—caused by mutations in the ADH receptor gene or the aquaporin-2 gene.

TABLE 4-8 Response to the Water Deprivation Test

	Increase in Urine Osmolality Above 295 mOsm/kg With Dehydration	Further Response to ADH
Normal patients	+	−
Central diabetes insipidus patients	−	+
Nephrogenic diabetes insipidus patients	−	−

B. Clinical Features

1. Polyuria is a hallmark finding: defined as urine output >3 L/day; urine is often very dilute.
2. Thirst and polydipsia—hydration is maintained if the patient is conscious and has access to water.
3. Hypernatremia is usually mild unless the patient has an impaired thirst drive or unable to access free water.

Quick HIT

- Primary polydipsia is usually seen in patients with psychiatric illnesses.
- If the patient is deprived of water, urine osmolarity will increase appropriately.

C. Diagnosis

1. Urine—low specific gravity and low osmolality indicate DI
2. Plasma osmolality
   a. Normal: 275 to 295 mOsm/kg
   b. Primary polydipsia: usually <257 mOsm/kg

   c. DI: usually >295 mOsm/kg
3. A water deprivation test (dehydration test) is required to make the diagnosis (see Table 4-8).
   a. Procedure
      - Withhold fluids, and measure serum osmolality, urine osmolality, and serum sodium every hour.
      - When serum sodium >145 mEq/L and serum osmolality >295 mOsm/kg, inject desmopressin subcutaneously or intravenously. Measure urine osmolality 1 hour later.
   b. Response—see Table 4-8
4. ADH level (not the test of choice; takes a long time to get results)
   a. Low in central DI
   b. Normal or elevated in nephrogenic DI

D. Treatment

1. Central DI
   a. Desmopressin (DDAVP) is the primary therapy and can be given by nasal spray, orally, or by injection.
   b. Other medications that enhance effect of ADH on kidney: chlorpropamide and carbamazepine.
   c. Treat the underlying cause.
   d. Monitor for development of hyponatremia.
2. Nephrogenic DI—treat with sodium restriction and thiazide diuretics.
   a. These deplete the body of sodium and cause mild volume depletion, which leads to increased reabsorption of sodium and water in the proximal tubules.
   b. The reabsorption of sodium and water in the proximal tubules means that less water reaches the distal tubules, leading to decreased urine volume and increased water retention.

A 28-year-old man with a history of type I diabetes presents with polydipsia and polyuria for the last 5 weeks. The patient reports that his blood glucose levels have been well controlled on his current insulin regimen. The patient denies tobacco, alcohol, or drug use and has no other past medical history. He has a temperature of 36.8°C, blood pressure of 114/68 mmHg, heart rate of 96 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air. The patient reports that he has fasted for the visit and laboratory results reveal the following.

Sodium	147 mEq/L
Potassium	3.8 mEq/L
Chloride	104 mEq/L
Bicarbonate	28 mEq/L
Blood urea nitrogen	16 mg/dL
Creatinine	1.1 mg/dL
Glucose	96 mg/dL
Serum osmolality before water deprivation test	310 mOsm/kg
Urine osmolality before water deprivation test	98 mOsm/kg
Serum osmolality after water deprivation test	322 mOsm/kg
Urine osmolality after water deprivation test	101 mOsm/kg

Desmopressin was administered and 30 minutes later the urine osmolality is 432 mOsm/kg.

Which of the following is this patient’s diagnosis?

A. Primary polydipsia
B. Central diabetes insipidus
C. Nephrogenic diabetes insipidus

D. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

- **The answer is (B): Central diabetes insipidus.** The patient in this question presents with polyuria and polydipsia with a normal serum glucose level. Given the patient's hypernatremia, low urine osmolality, and elevated serum osmolality, the patient likely has diabetes insipidus (DI) and it now remains to distinguish between central and nephrogenic DI. **(A, D)** Primary polydipsia and SIADH are causes of hyponatremia, not hypernatremia. A water deprivation test with desmopressin can help differentiate central DI from nephrogenic DI. The patient in this question has a urine osmolality that increased about 400% after desmopressin, establishing the diagnosis as central DI.

Syndrome of Inappropriate Secretion of Antidiuretic Hormone

A. General Characteristics

1. Pathophysiology
   a. Excess ADH is secreted from the posterior pituitary or an ectopic source. Elevated levels lead to free water retention and excretion of concentrated urine. This has two major effects: hyponatremia and volume expansion.
   b. **Despite volume expansion, edema is not seen in syndrome of inappropriate secretion of antidiuretic hormone (SIADH).** This is because natriuresis (excretion of excessive sodium in urine) occurs despite hyponatremia.
   c. Reasons for natriuresis
      - Volume expansion causes an increase in atrial natriuretic peptide (ANP) which increases urine sodium excretion.
      - Volume expansion leads to a decrease in proximal tubular sodium absorption.
      - The renin–angiotensin–aldosterone system is inhibited, and thus sodium is excreted in the urine.

Quick HIT

In SIADH, volume expansion occurs due to water retention, but edema is prevented due to natriuresis.

Quick HIT

Hyponatremia Pearls

- Hypovolemic hyponatremia—volume contracted
- Hypervolemic hyponatremia—volume expanded with edema, but low effective arterial blood volume
- SIADH—euvolemic

B. Causes

1. Malignancy (e.g., lung, pancreas, prostate, bladder, lymphoma, leukemia)
2. CNS disorders (e.g., stroke, head trauma, infection, psychosis)
3. Pulmonary disorders (e.g., pneumonia, asthma, acute respiratory failure, pneumothorax)
4. Positive pressure ventilation
5. Drugs (many, including selective serotonin reuptake inhibitors [SSRIs], chlorpropamide, oxytocin, morphine, desmopressin, vincristine, cyclophosphamide, MDMA)
6. Postoperative state (e.g., as a result of anesthesia, pain, or stress)

C. Clinical Features

1. Acute hyponatremia—Osmotic water shifts lead to increased intracellular fluid volume. Signs and symptoms are secondary to cerebral edema and are primarily neurologic
   a. Nausea and malaise (mild)
   b. Headache, lethargy
   c. **Can lead to seizures, coma, or death if untreated**
2. Chronic hyponatremia
   a. May be asymptomatic
   b. Fatigue, anorexia, nausea, and vomiting

c. CNS symptoms are less common because chronic loss of sodium and potassium from brain cells decreases brain edema (due to secondary water shifts from ICF to ECF)

D. Diagnosis

1. **SIADH is a diagnosis of exclusion** after other causes of hyponatremia have been ruled out. The following help in supporting the diagnosis:
   a. Hyponatremia with inappropriately concentrated urine (high urine sodium and osmolality); plasma osmolality <275 mOsm per kg
   b. Low serum uric acid level <4 mg/dL
   c. Low BUN
   d. Normal thyroid and adrenal function, as well as renal, cardiac, and liver function
   e. Euvolemic state

Quick HIT

Major characteristics of SIADH
- Hyponatremia
- Euvolemia
- Natriuresis
- Hypouricemia and low BUN
- Normal thyroid and adrenal function

E. Treatment

1. Correct the underlying cause, if known.
2. For asymptomatic patients
   a. Water restriction is usually sufficient
   b. Oral salt tablets with or without loop diuretic (high solute load promotes urine output; loop diuretic interferes with renal concentrating ability)
   c. Oral urea packets (high solute load as above)
   d. Vasopressin receptor antagonists (e.g., tolvaptan) can be used in select patients, but have high cost and risk of overly rapid correction of hyponatremia
3. For symptomatic patients, approach varies depending on severity of neurologic symptoms

a. Restrict water intake
b. Give hypertonic saline for severe symptoms (e.g., seizures, coma). These patients require close monitoring in an intensive care unit

4. Do not raise the serum sodium concentration too quickly if hyponatremia is chronic (or chronicity is unknown). Rapid flux of water into the extracellular fluid can result in osmotic demyelination syndrome (formerly known as central pontine myelinolysis). A general guideline is that the serum sodium should not increase by more than 4 to 6 mEq/L in the first 24 hours. More rapid correction (e.g., 4 to 6 mEq/L over 6 hours or less) is indicated if hyponatremia is acute or patient has severe symptoms

Diseases of the Parathyroid Glands

Hypoparathyroidism

A. Causes

1. Postsurgical hypoparathyroidism is most common. Removal of glands during head and neck surgery account for the majority of cases—thyroidectomy, parathyroidectomy, radical surgery for head and neck malignancies.
2. Nonsurgical hypoparathyroidism is rare. Causes include autoimmune destruction of parathyroid glands, infiltrative diseases, and radiation.

Quick HIT

Pseudohypoparathyroidism

- End-organ resistance to the action of PTH
- Laboratory value findings: hypocalcemia, hyperphosphatemia, high PTH

B. Clinical Features

1. Cardiac arrhythmias
2. Rickets and osteomalacia

3. Increased neuromuscular irritability due to hypocalcemia
   a. Numbness and paresthesias—perioral, fingers, toes
   b. Fatigue, anxiety, and depression
   c. Tetany
      - Hyperactive deep tendon reflexes
      - *Chvostek sign*—Tapping the facial nerve elicits contraction of facial muscles.
      - *Trousseau sign*—Inflating the BP cuff to a pressure higher than the patient's systolic BP for 3 minutes elicits carpal spasms
   d. Focal or generalized seizures
4. Basal ganglia calcifications, which may cause parkinsonism or other movement disorders
5. **Prolonged QT interval** on ECG—Hypocalcemia should always be in the differential diagnosis of a prolonged QT interval
6. Cataracts

C. Diagnosis

1. Low serum calcium
2. High serum phosphate
3. Serum PTH inappropriately low

D. Treatment

1. IV calcium gluconate in severe cases, oral calcium in mild to moderate cases
2. Vitamin D supplementation (calcitriol)
3. Note that both vitamin D and calcium replacement can increase urinary calcium excretion, precipitating kidney stones. Therefore, administer with caution to avoid hypercalciuria. The goal is to keep serum calcium at >7.5 mg/dL while balancing symptom control and hypercalciuria
4. Recombinant PTH (not first-line therapy due to high cost and uncertainty about long-term safety)

Primary Hyperparathyroidism

A. General Characteristics

1. One or more glands produce inappropriately high amounts of PTH relative to the serum calcium level.
2. Most common cause of hypercalcemia in the outpatient setting.

B. Causes

1. Adenoma (85% of cases)—majority involve only one gland
2. Hyperplasia (less than 10% of cases)—all four glands usually affected
3. Carcinoma (1% to 2% of cases)

C. Clinical Features

1. *"Stones"*
   a. Nephrolithiasis
   b. Nephrocalcinosis
2. *"Bones"*
   a. Bone aches and pains
   b. **Osteitis fibrosa cystica ("brown tumors")**—predisposes patient to pathologic fractures (Figure 4-8)
3. *"Groans"*
   a. Muscle pain and weakness
   b. Pancreatitis
   c. Peptic ulcer disease
   d. Gout and pseudogout
   e. Constipation
4. *"Psychiatric overtones"*—depression, fatigue, sleep disturbances, anxiety, lethargy
5. Other symptoms:
   a. Polydipsia, polyuria
   b. HTN, shortened QT interval
   c. Weight loss
   d. Renal insufficiency
   e. Nephrogenic diabetes insipidus

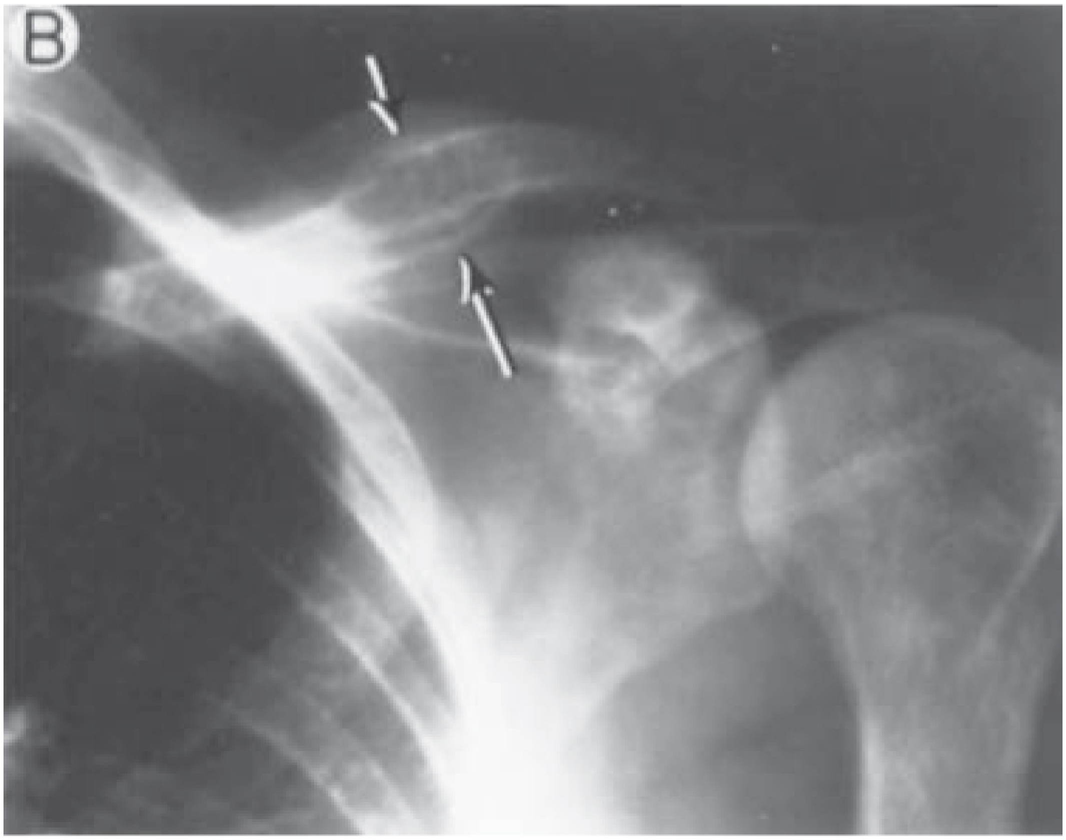


FIGURE 4-8 **X-ray of the clavicle in a patient with osteitis fibrosa cystica ("brown tumors"), a disease in which cystic bone spaces are filled with brown fibrous tissue. Brown tumors predispose patients to pathologic fractures.**
(Reprinted with permission from Becker KL, Bilezikian JP, Brenner WJ, et al. *Principles and Practice of Endocrinology and Metabolism*. 3rd ed. Lippincott Williams & Wilkins; 2001.)

D. Diagnosis

1. Laboratory (see also Clinical Pearl 4-11)
   a. Calcium levels (hypercalcemia)—when calculating calcium levels, be aware of albumin levels. Calculate the corrected calcium or directly measure an ionized calcium level
   b. PTH levels
      - Should be elevated or inappropriately normal given degree of hypercalcemia
      - Note that in the presence of hypercalcemia, a normal PTH level is "abnormal" (i.e., normal is still too high) because high calcium levels should suppress PTH secretion

c. Hypophosphatemia
d. 24-hour urinary calcium excretion (to differentiate between primary hyperparathyroidism and familial hypocalciuric hypercalcemia or FHH)
e. Chloride/phosphorus ratio of >33 is supportive of primary hyperparathyroidism **(33-to-1 rule).** Chloride is high secondary to renal bicarbonate wasting, a direct effect of PTH

2. Radiographs
   a. Subperiosteal bone resorption usually on radial aspect of second and third phalanges, but can appear in any location
   b. Osteopenia

CLINICAL PEARL 4-11

Secondary Hyperparathyroidism

- Characterized by an elevated concentration of PTH and a low or low-normal serum calcium level.
- Caused by chronic renal failure (most common cause), as well as vitamin D deficiency and renal hypercalciuria.
- Treatment depends on the cause: if vitamin D deficiency, give vitamin D; if renal failure, give calcitriol and oral calcium supplements plus dietary phosphorus restriction.

E. Treatment

1. Surgical removal is the only definitive treatment, but not all patients require it. If the patient is over 50 years of age and is asymptomatic (with normal bone mass and renal function), surgery may not be needed.
   a. Primary hyperparathyroidism due to hyperplasia—All the four glands are removed. A small amount of parathyroid tissue is placed in the forearm muscle to retain parathyroid function. If hyperplasia recurs postoperatively, surgery is then limited to the arm and will not involve the neck.
   b. Primary hyperparathyroidism due to adenoma—Surgical removal of the adenoma is curative.

c. Primary hyperparathyroidism due to carcinoma—Remove the tumor, ipsilateral thyroid lobe, and all enlarged lymph nodes.

2. Medical treatment: for patients who are not surgical candidates (or who decline surgery) but have symptomatic hypercalcemia, calcimimetic agents (e.g., cinacalcet) can be used to normalize serum calcium levels. These work by inhibiting PTH secretion. Bisphosphonates may be used for osteoporosis.

Quick HIT

Relative Indications for Surgery in Primary Hyperparathyroidism

- Age <50 years
- Marked decrease in bone mass or vertebral fracture
- Nephrolithiasis, renal insufficiency
- Markedly elevated serum calcium level or episode of severe hypercalcemia
- Urine calcium >400 mg in 24 hours

A 64-year-old man with a history of hypertension and a 30-pack-year smoking history presents with unrelenting abdominal pain and constipation. He also endorses nausea and his partner reports that he has exhibited subtle signs of mental deterioration. He has a temperature of 36.8°C, blood pressure of 118/72 mmHg, heart rate of 98 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 96% on room air. Physical examination is unremarkable and laboratory studies reveal the following.

Calcium	15.1 mg/dL
Albumin	3.9 g/dL
Serum parathyroid hormone	8 pg/mL
1,25-dihydroxyvitamin D	13 pm/mL (normal range, 15.9–55.6 pg/mL)

What additional laboratory value do you expect to find with this patient's condition?

A. Increased angiotensin-converting enzyme (ACE) blood levels
B. Decreased interleukin-6 levels
C. Decreased urine calcium levels
D. Increased levels of parathyroid hormone–related protein

- **The answer is D: Increased levels of parathyroid hormone–related protein.** The patient in this question presents with classic features of hypercalcemia (polyuria, nausea, vomiting, polydipsia, constipation, and cognitive dysfunction). His serum calcium is elevated with a suppressed serum parathyroid hormone (PTH) level. In addition, the history of extensive smoking gives an important clue that hypercalcemia of malignancy should be highly considered here. With hypercalcemia of malignancy, serum calcium levels are much more elevated than in patients with primary hyperparathyroidism. **(B)** In hypercalcemia of malignancy, osteolytic metastases may

contribute to the markedly elevated calcium level, but you would also expect secretion of parathyroid hormone–related protein (PTH-rP) in addition to increased interleukin-6 levels. **(A)** Increased angiotensin-converting enzyme (ACE) blood levels is often seen in sarcoidosis; however, this patient has low 1,25-dihydroxyvitamin D levels and you would expect elevated levels in sarcoidosis due to the increased conversion in granulomatous tissue. **(C)** Decreased urine calcium levels are seen in familial hypercalcemia hypocalciuria; however, this would be accompanied by high-to-normal PTH levels (and this patient has suppressed serum PTH levels).

Diseases of the Adrenal Glands

Cushing Syndrome

A. General Characteristics

1. Cushing **syndrome** results from excessive levels of glucocorticoids due to any cause. Cortisol is the principal glucocorticoid.
2. Cushing **disease** results from an ACTH-secreting pituitary adenoma, thus a pituitary cause of Cushing syndrome (see below).

B. Causes

1. Iatrogenic Cushing syndrome is the most common cause, and is due to prescribed glucocorticoids. Androgen excess is absent because the exogenous steroid suppresses androgen production by the adrenals
2. Cushing disease is the second most common cause and leads to bilateral adrenal hyperplasia. Androgen excess is common
3. Adrenal adenomas and carcinomas (20% of cases)
4. Ectopic ACTH production (10% to 15%)
   a. ACTH-secreting neuroendocrine tumor stimulates the cortisol release from the adrenal glands without the normal negative feedback loop because the source of the ACTH is outside the pituitary gland

b. Most often caused by neuroendocrine tumors of the lung (e.g., small cell carcinoma), pancreas, or thymus

Quick HIT

Effects of Cortisol (generally catabolic)

- Impaired collagen production, enhanced protein catabolism
- Anti-insulin effects (leading to glucose intolerance)
- Impaired immunity (has inhibitory effects on PMNs, T cells)
- Enhances catecholamine activity (HTN)

C. Clinical Features

1. Changes in appearance: central obesity, hirsutism, round face, dorsal fat pad, purple striae on abdomen, lanugo hair, acne, easy bruising
2. HTN
3. Decreased glucose tolerance (diabetes)
4. Hypogonadism—menstrual irregularity, decreased libido, and infertility
5. Androgen excess in females (see Figure 4-9)—only seen in ACTH-dependent forms
6. Musculoskeletal—proximal muscle wasting and weakness due to protein catabolism, osteoporosis, aseptic necrosis of femoral head especially with exogenous steroid use
7. Psychiatric disturbances—depression, anxiety, mania
8. Increased likelihood of infections (due to impaired immunity)

Quick HIT

Some signs and symptoms in patients with high cortisol (e.g., obesity, HTN, osteoporosis, DM) are nonspecific and less helpful in diagnosing the patient. On the other hand, easy bruising, typical striae, myopathy, and virilizing signs are more helpful in diagnosis.

D. Diagnosis

1. Initial screening (Table 4-9). Two of three following tests need to be positive in order to give the diagnosis of Cushing syndrome:

a. An overnight, low-dose dexamethasone suppression test is the initial screening test. Give the patient 1 mg of dexamethasone at 11 pm. Measure the serum cortisol level at 8 am.
   - If the serum cortisol is <2 mcg/dL, Cushing syndrome can be excluded. This test is very sensitive.
   - If the serum cortisol is >2 mcg/dL, the patient has Cushing syndrome. Order a high-dose dexamethasone suppression test to determine whether the cause is Cushing disease, an adrenal tumor, or an ectopic ACTH tumor.

b. The 24-hour urinary free cortisol level is another excellent screening test; values greater than three times normal are rare except in Cushing syndrome.

c. Late night salivary cortisol; saliva collected prior to patient's bedtime. Upper limits of normal and concentrations for diagnosis will depend on commercial assay used. This measurement should be done twice.

FIGURE 4-9 **Androgen excess manifesting as masculinization in an individual with (46,XX) chromosomes, only seen in ACTH-dependent forms of Cushing syndrome.**
(Reprinted with permission from Rubin E. *Essential Pathology*. 3rd ed. Lippincott Williams & Wilkins; 2000.)

TABLE 4-9 Response to Diagnostic Tests in Cushing Syndrome

Healthy patient	• Normal cortisol/normal ACTH • Suppression with low-dose dexamethasone • Suppression with high-dose dexamethasone • Mild increase with CRH test
Cushing disease	• High cortisol/high ACTH • No suppression with low-dose dexamethasone • Suppression with high-dose dexamethasone • Great increase in cortisol with CRH test
Adrenal tumor	• High cortisol/low ACTH • No suppression with low-dose dexamethasone • No suppression with high-dose dexamethasone • No change after CRH test
Ectopic ACTH-producing tumor	• High cortisol/high ACTH • No suppression with low-dose dexamethasone • No suppression with high-dose dexamethasone • No change after CRH test

2. ACTH level—Once you establish a diagnosis of Cushing syndrome, measure the ACTH level on two occasions. If it is low, the cause of high cortisol levels is likely an adrenal tumor or hyperplasia, not a pituitary disease or an ectopic ACTH-producing tumor.
3. High-dose dexamethasone suppression test. Give patient 8 mg of dexamethasone at 11 pm. Measure the serum cortisol level at 8 am.
   a. In Cushing disease, the result is suppression (>50%) in cortisol levels.
   b. If cortisol suppression does **not** occur and plasma ACTH levels are high, an ectopic ACTH-producing tumor is likely the diagnosis.
4. CRH stimulation test—CRH is administered intravenously.
   a. If ACTH/cortisol levels increase (deemed a "response"), then Cushing disease is the diagnosis.
   b. If ACTH/cortisol levels do not increase (deemed "no response"), then the patient has either ectopic ACTH secretion or an adrenal tumor.
5. Once hormonal studies have established the site of disease, imaging is the next step (CT scan or MRI).

Quick HIT

Patients with **Cushing disease** may have **hyperpigmentation** due to elevated ACTH levels, whereas patients with Cushing syndrome due to other causes will not have hyperpigmentation (hyperpigmentation is caused by increased ACTH, not cortisol).

E. Treatment

1. Iatrogenic Cushing syndrome: tapering of glucocorticoid
2. Cushing disease (ACTH-producing pituitary tumor): surgery (transsphenoidal resection of pituitary adenoma)—usually safe and effective
3. Adrenal adenoma or carcinoma: surgery (adrenalectomy)
4. When surgery is contraindicated or unsuccessful, or patient is awaiting surgical treatment, medical therapies are appropriate. Adrenal enzyme inhibitors (such as ketoconazole) inhibit the synthesis of cortisol and thus can be used as medical therapy

A 48-year-old woman presents with weight gain, easy bruisability, and muscle weakness. She has a 30-pack-year history of smoking. She presents with a temperature of 36.8°C, blood pressure of 144/92 mmHg, heart rate of 96 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air. Laboratory studies are significant for a fasting blood glucose of 310 mg/dL, a 24-hour urine cortisol level of 1,200 µg (normal range, 10 to 100 µg), and a plasma ACTH of 126 pg/mL (normal range, 10 to 60 pg/mL). Twenty-four–hour urine cortisol level is 1,184 µg after high-dose dexamethasone is administered.

Which of the following is the cause of the patient's symptoms and laboratory findings?

A. Exogenous steroids
B. Adrenocortical adenoma
C. Ectopic ACTH-producing tumor
D. Cushing disease

- **The answer is C: Ectopic ACTH-producing tumor.** The patient in this question is presenting with typical symptoms of Cushing syndrome. In addition to weight gain, easy bruisability, and muscle weakness, symptoms include round face, truncal obesity, dorsal fat pad, hyperglycemia, osteoporosis, amenorrhea, and hypertension. Cushing syndrome by definition only signifies increased cortisol levels, so there must be a workup to determine the etiology of the disorder. Once the diagnosis of Cushing syndrome has been made, the etiology must then be determined by measuring plasma ACTH level (elevated ACTH is considered greater than 20 pg/mL). **(A)** The most common cause of Cushing syndrome is exogenous steroids; however, this will have a low ACTH level due to the steroids negatively inhibiting secretion of ACTH from the pituitary. **(B)** Likewise, adrenal-related causes of Cushing syndrome such as adrenocortical adenoma will have a decreased ACTH level. This

patient presents with an elevated ACTH level and so then next step is to distinguish between Cushing disease (increased ACTH secretion from a pituitary adenoma) and ectopic ACTH production, sometimes seen in small cell lung cancer. **(D)** High-dose dexamethasone will normally suppress urinary cortisol or serum cortisol levels in Cushing disease, but will not suppress cortisol levels in ectopic ACTH production. In this patient, 24-hour urine cortisol levels were not adequately suppressed (defined as suppressing cortisol levels by at least 50%), so ectopic ACTH production (likely small cell lung cancer given the patient's smoking history) is the diagnosis.

Pheochromocytoma

A. General Characteristics

1. Pheochromocytomas are rare tumors that produce, store, and secrete catecholamines.
2. Ninety percent found in adrenal medulla (10% extra-adrenal).
3. Curable if diagnosed and treated, but **may be fatal if undiagnosed.**
4. Arise from the chromaffin cells of the adrenal medulla or from the sympathetic ganglia if extra-adrenal.

Quick HIT

Any 24-hour urine collection (i.e., 24-hour urine collection of metanephrines and catecholamines for pheochromocytoma) should also test the amount of urine creatinine to determine if the patient has provided an appropriate sample.

B. Clinical Features

1. HTN—BP is persistently high, with episodes of severe HTN (paroxysmal)
2. Severe pounding headache
3. Inappropriate severe sweating
4. Tachycardia with palpitations
5. Anxiety

6. Feeling of impending doom
7. Some may be asymptomatic if detected early (incidentally found on CT or MRI)
8. Laboratory findings: hyperglycemia, hyperlipidemia, hypokalemia

C. Diagnosis

1. Urine screen—test for the presence of the following breakdown products of catecholamines:
   a. 24-hour urine metanephrines
   b. Plasma fractionated metanephrines
2. Plasma metanephrines have been proposed by some groups as a superior test to rule out pheochromocytoma, especially when clinical suspicion is high
3. Tumor localization imaging—CT or MRI of the abdomen and pelvis
   a. Other imaging: If CT or MRI is negative but biochemical testing confirms suspicion
      - Fludeoxyglucose-positron emission tomography (FDG-PET/CT): more sensitive than CT or MRI for detecting metastatic disease
      - Gallium-68 DOTATATE PET: radiotracer binds to cells that express somatostatin receptors
      - Iobenguane I-123 scintigraphy (also known as MIBG): compound resembling norepinephrine is injected and taken up by adrenergic tissue

Quick HIT

Historical Rule of 10s for Pheochromocytoma Tumors

- 10% are familial
- 10% are bilateral (suspect MEN type II)
- 10% are malignant
- 10% are multiple
- 10% occur in children
- 10% are extra-adrenal (more often malignant)—The most common site is the organ of Zuckerkandl, which is located at the aortic bifurcation.
- **The “rules of 10” have since been challenged by recent evidence**: 30% are familial, up to 50% can be bilateral, 25% are extra-adrenal, and malignancy risk varies greatly by location and genetic mutations.

D. Treatment

1. Surgical tumor resection with early ligation of venous drainage is the treatment of choice. Ligation lowers the possibility of catecholamine release/crisis by tying off drainage.
   a. Patients should be treated with α-blockade (typically **phenoxybenzamine**) for 7 to 14 days prior to surgery, followed by β-blockade (i.e., propranolol) for 2 to 3 days prior to surgery.
   b. The α-blockade is used to control BP, and the β-blockade is used to decrease tachycardia. β-Blockade should never be started first, because this can lead to unopposed α-adrenergic receptor stimulation and hypertensive crisis.
   c. Laparoscopic adrenalectomy can be safely performed for most small- to medium-sized pheochromocytomas.

Quick HIT

Consider pheochromocytoma as the diagnosis if the following are present:
- Headache
- Profuse sweating
- Palpitations
- Tachycardia
- Apprehension or sense of impending doom

Primary Hyperaldosteronism

A. General Characteristics

1. Excessive production of aldosterone by the adrenal glands independent of any regulation by the renin–angiotensin system (see also Clinical Pearl 4-12)
2. Excess mineralocorticoids increase the activity of the Na+/K+ pumps in the cortical collecting tubules.
   a. Sodium retention causes ECF volume expansion and HTN.
   b. Potassium loss can result in hypokalemia (although this is not always present).
3. Excess aldosterone also increases the secretion of hydrogen ions into the lumen of the medullary collecting tubules resulting in metabolic

alkalosis.

Quick HIT

Always suspect hyperaldosteronism in a hypertensive patient with hypokalemia who is not on a diuretic.

B. Causes

1. Bilateral idiopathic adrenal hyperplasia (two-thirds of cases)
2. Adrenal adenoma (in one-third of cases)—aldosterone-producing adenoma (**Conn syndrome**)
3. Adrenal or ectopic aldosterone-producing carcinoma (in <1% of the cases)

CLINICAL PEARL 4-12

Multiple Endocrine Neoplasia (MEN) Syndrome

- Rare inherited condition with the propensity to develop multiple endocrine tumors.
- Autosomal dominant inheritance with incomplete penetrance.
- Types
  - **MEN type I**—“3 Ps”
    - **P**arathyroid hyperplasia (in 90% of the patients with MEN I)
    - **P**ancreatic islet cell tumors (in two-thirds of the patients with MEN I)—ZES (50%), insulinoma (20%)
    - **P**ituitary adenomas (in two-thirds of the patients with MEN I)
  - **MEN type IIA**—“MPH”
    - **M**edullary thyroid carcinoma (in 100% of the patients with MEN IIA)
    - **P**heochromocytoma (in more than one-third of the patients with MEN IIA)
    - **H**yperparathyroidism (in 50% of the patients with MEN IIA)
  - **MEN type IIB**—“MMMP”
    - **M**ucosal neuromas (in 100% of the patients with MEN IIB)—in the nasopharynx, oropharynx, larynx, and conjunctiva
    - **M**edullary thyroid carcinoma (in 85% of the patients with MEN IIB)—more aggressive than in MEN IIA
    - **M**arfanoid body habitus
    - **P**heochromocytoma

C. Clinical Features

1. HTN (most common clinical feature); may otherwise be asymptomatic
2. Headache, fatigue, weakness
3. Polydipsia, nocturnal polyuria (due to hypokalemia)
4. **Absence of peripheral edema**

D. Diagnosis

1. Ratio of the plasma aldosterone level to plasma renin—A screening test in primary hyperaldosteronism reveals inappropriately elevated levels of plasma aldosterone with coexistent decreased plasma renin activity. Therefore, if the plasma aldosterone-to-renin ratio is >30, evaluate further.
2. For definitive diagnosis, one of the two tests is usually performed.
   a. Saline infusion test
      - Infusion of isotonic saline will decrease aldosterone levels in normal patients but not in those with primary aldosteronism.
      - If aldosterone levels are <5 ng/dL after saline infusion, primary aldosteronism may be ruled out.

   b. Oral sodium loading
      - The patient is given a high-salt diet for 3 days. Serum and urine electrolytes, aldosterone, and creatinine are measured on the third day. High urine aldosterone in the setting of high urine sodium (to document appropriate sodium loading) confirms the diagnosis.
3. To diagnose the cause of primary aldosteronism:
   a. Adrenal CT is the initial test of choice to distinguish between adrenal adenoma versus hyperplasia and rule out adrenal carcinoma.
   b. Adrenal venous sampling for aldosterone levels—A high level of aldosterone on one side indicates an adenoma. High levels on both sides indicate bilateral hyperplasia. Indicated for patients pursuing surgical management (e.g., unilateral adrenalectomy).

Quick HIT

The prevalence of **adrenal incidentaloma** is on the rise with the more widespread use of imaging techniques. An adrenal incidentaloma is a nonfunctioning adrenal tumor. Most are benign, but the risk of malignancy increases with increasing size. Treat by first ruling out a functioning tumor and then resect any hormonally functioning tumors, tumors greater than 4 cm, or tumors with rapid growth rate (risk of malignant disease).

Quick HIT

It is important to distinguish adenoma from hyperplasia because HTN associated with hyperplasia is **not** benefited by bilateral adrenalectomy, whereas HTN associated with adenoma is usually improved/cured by removal of the adenoma.

E. Treatment

1. For adenoma—Surgical resection (adrenalectomy) is often curative.
2. For bilateral hyperplasia
   a. Mineralocorticoid antagonists (e.g., spironolactone) inhibit the action of aldosterone
   b. Surgery is usually not indicated

Adrenal Insufficiency

A. Causes

1. Primary adrenal insufficiency (**Addison disease**)—at level of adrenal gland
   a. Idiopathic (thought to be autoimmune disease) is the most common type in the industrialized world
   b. Infectious diseases—these include tuberculosis (most common cause worldwide) and fungal infections. Causes also include cytomegalovirus, HIV, histoplasmosis, and syphilis
   c. Iatrogenic—for example, a bilateral adrenalectomy
   d. Metastatic disease—from lung, breast, stomach, colon cancer, or lymphoma

e. Adrenal hemorrhage or infarction
f. Drugs: ketoconazole, fluconazole, rifampin, phenytoin, among others

2. Secondary adrenal insufficiency—at level of pituitary
   a. Medications: high-dose progestins (e.g., megestrol acetate), and chronic opioids.
   b. Hypopituitarism (rare)—due to a variety of insults.

Quick HIT

The most common cause of Addison disease worldwide is tuberculosis; autoimmune disease is the most common cause in the industrialized world. However, the most common cause of adrenal insufficiency overall (99% of all cases) is abrupt cessation of exogenous glucocorticoids.

3. Tertiary adrenal insufficiency—at level of hypothalamus
   a. Most commonly caused by long-term high-dose glucocorticoid therapy. High doses of glucocorticoids decrease hypothalamic CRH secretion (and decrease ACTH secretion). When these patients develop a serious illness or undergo trauma, they cannot release an appropriate amount of cortisol because of chronic suppression of CRH and ACTH by exogenous glucocorticoids. Therefore, symptoms of adrenal insufficiency result.

Quick HIT

Most Common Clinical Findings of Adrenal Insufficiency

- Weight loss
- Weakness
- Hyperpigmentation (only occurs in primary adrenal insufficiency)
- Anorexia
- Nausea
- Postural hypotension
- Abdominal pain
- Hypoglycemia
- Hyponatremia

B. Clinical Features

1. Lack of cortisol
   a. GI symptoms—anorexia, nausea and vomiting, vague abdominal pain, weight loss
   b. Psychiatric symptoms—depression, lethargy, confusion, psychosis.
   c. **Hypoglycemia**—Cortisol is a gluconeogenic hormone.
   d. **Hyperpigmentation**
      - This is a common finding in primary adrenal insufficiency; not seen in secondary or tertiary adrenal insufficiency. In secondary and tertiary adrenal insufficiency, ACTH levels are low, not high.
      - Low cortisol stimulates ACTH and MSH secretion.
   e. Intolerance to physiologic stress is a feared complication.
   f. In women, decreased libido and amenorrhea may occur.
2. Low aldosterone (only seen in primary adrenal insufficiency because aldosterone depends on the renin–angiotensin system, not ACTH). Results in:
   a. Sodium and volume loss, which may lead to:
      - Hyponatremia
      - Hypotension, decreased cardiac output, and decreased renal perfusion
      - Weakness, shock, and syncope
   b. Hyperkalemia (due to retention of potassium)

Quick HIT

Hyperpigmentation and hyperkalemia appear in **primary**, not secondary, adrenal insufficiency.

Quick HIT

The most common presentation of tertiary adrenal insufficiency is a patient who has been on long-term steroids who stops them suddenly (i.e., for surgery) or who has an increased need (infection). Treatment is easy—give corticosteroids until the patient is stable clinically.

C. Diagnosis

1. Decreased morning serum cortisol level (Figure 4-10).
2. Plasma ACTH level—if low, this implies a secondary or tertiary adrenal insufficiency (ACTH-dependent cause).
3. Standard ACTH stimulation test
   a. This is a definitive test for primary adrenal insufficiency; give an IV infusion of synthetic ACTH (cosyntropin), and measure serum cortisol 30 or 60 minutes after the infusion.
   b. A normal rise in cortisol excludes primary adrenal insufficiency, and most cases of secondary adrenal insufficiency.
   c. In primary adrenal insufficiency, cortisol does not increase sufficiently.
   d. In secondary adrenal insufficiency, especially when chronic, cortisol fails to respond to ACTH infusion, as in primary adrenal insufficiency (the adrenals are not used to being stimulated, so they do not respond right away). However, if recent onset, the adrenals may still partially response to ACTH stimulation. In these cases, repeat testing may be needed.
4. Perform imaging tests (MRI of brain—pituitary/hypothalamus) if secondary or tertiary adrenal insufficiency is diagnosed

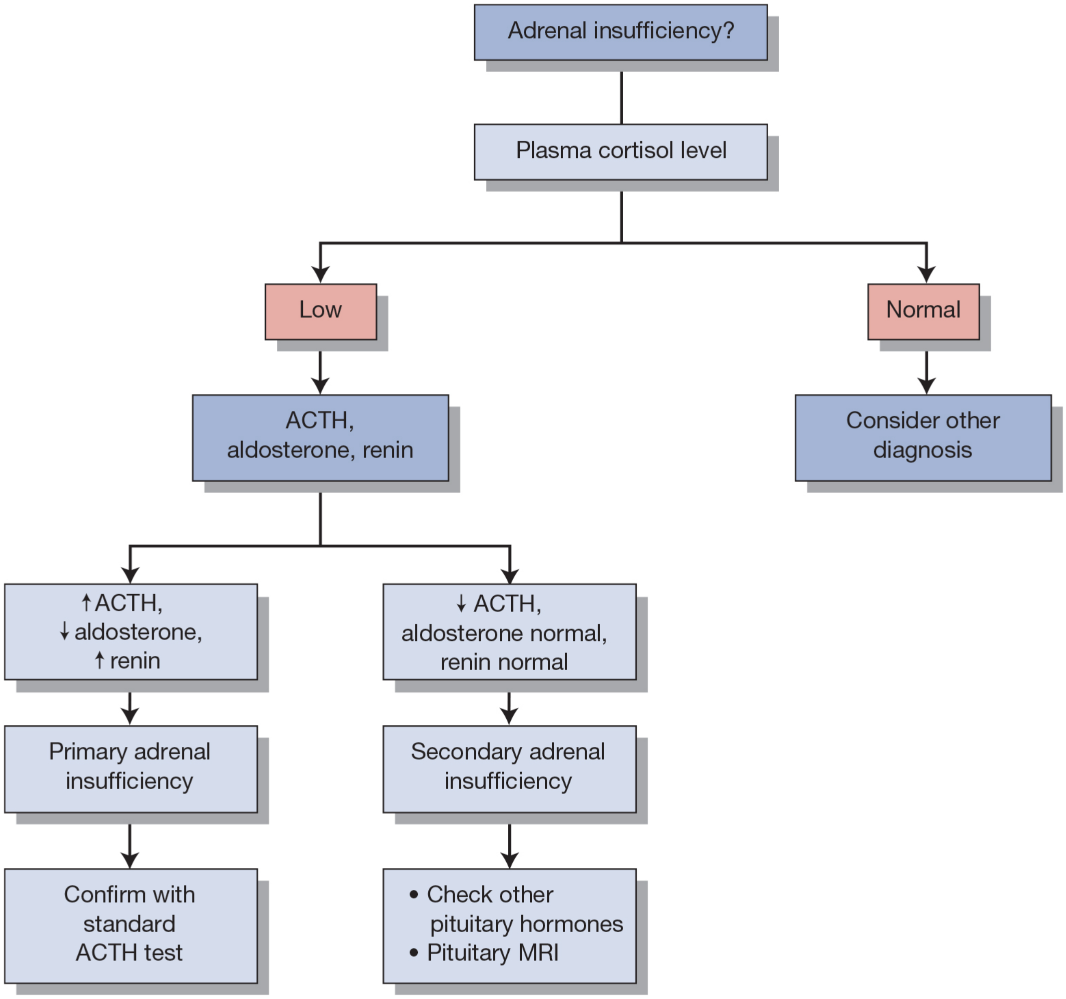


FIGURE 4-10 **Algorithm for the diagnosis of adrenal insufficiency.** (Adapted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:2730. Figure 407-5.)

CLINICAL PEARL 4-13

Adrenal Crisis

- An acute and severely symptomatic stage of adrenal insufficiency that can include severe hypotension and cardiovascular collapse, abdominal pain (can mimic an acute abdomen), acute renal failure, and death.
- Any stress (e.g., trauma, infection, surgery) can precipitate an adrenal crisis.
- Can be fatal if untreated.
- Treat with IV hydrocortisone, IV fluids (balanced crystalloid with 5% dextrose), and a search for the underlying condition that precipitated the crisis.

D. Treatment

1. Adrenal crisis is a life-threatening emergency. Treat with aggressive fluid resuscitation, IV hydrocortisone, and determine the underlying cause (see Clinical Pearl 4-13).
2. Primary adrenal insufficiency: daily oral glucocorticoid (hydrocortisone or prednisone) and daily fludrocortisone (mineralocorticoid).
3. Secondary adrenal insufficiency: same as in primary adrenal insufficiency, except that mineralocorticoid replacement is not necessary.
4. Patients must be counseled to increase the dose of glucocorticoid during periods of illness or surgery.

Quick HIT

Congenital adrenal hyperplasia (CAH) is a very treatable condition. Treat by replacing glucocorticoids and mineralocorticoid to reduce CRH and ACTH secretion.

Congenital Adrenal Hyperplasia

A. General Characteristics

1. Autosomal recessive disease.

2. Ninety percent of the cases are due to 21-hydroxylase deficiency. 11-Hydroxylase deficiency is the next most common cause.

B. Clinical Features

1. Decreased cortisol and aldosterone production are the main events. Increased ACTH secretion (due to the lack of negative feedback) causes adrenal overstimulation, and thus, hyperplasia
2. As precursors of cortisol and aldosterone build up, they are shunted toward the synthesis of androgens (e.g., DHEA, testosterone), causing virilization
3. Virilization with differences of sex development
   a. 46,XX infants are typically born with atypical genitalia with clitoral enlargement, labial fusion, and a urogenital sinus. Uterus, cervix, and ovaries are normal
   b. 46,XY infants usually have normal-appearing genitalia at birth
4. Salt wasting form (more severe form of disease)
   a. Emesis, dehydration, hypotension, and shock can develop in first 2 to 4 weeks of life
   b. **Hyponatremia and hyperkalemia** due to lack of aldosterone
   c. Hypoglycemia due to lack of cortisol

C. Diagnosis

1. High levels of **17-hydroxyprogesterone** in the serum. Neonatal screening for 21-hydroxylase deficiency is approved in all 50 states, leading to early diagnosis in many cases.

D. Treatment

1. Medically—Use glucocorticoids and mineralocorticoid replacement; this shuts off the excess ACTH secretion via negative feedback. Beware of undertreatment and overtreatment.
2. Atypical genitalia—multidisciplinary therapeutic plan should be developed with the patient and family with attention to psychosocial aspects of disorders of sex development. Some may opt for surgery during infancy or childhood, which is controversial. Gender identity (female, male, or nonbinary), sexual orientation, and desires for fertility may evolve over time.

Diseases of the Central and Peripheral Nervous Systems 5

Mark Duncan

Cerebrovascular Disease

Ischemic Stroke

A. General Characteristics

1. Epidemiology
   a. Stroke, or cerebrovascular accident (CVA), is the third most common cause of death in the United States.
   b. It is the **leading cause of neurologic disability.**
2. Classes of ischemic stroke
   a. Transient ischemic attack (TIA)—see below
   b. Thrombotic stroke
   c. Embolic stroke
   d. Ischemic from systemic hypoperfusion

Quick HIT

Types of Strokes

- Ischemic strokes (∼85% of cases)
- Hemorrhagic strokes (∼15% of cases)

3. TIAs (see Clinical Pearl 5-1)
   a. A TIA is a transient focal neurologic deficit that typically is short in duration and does not have any evidence of brain infarction.

- Previously defined using time as an endpoint, with symptoms lasting less than 24 hours.
- However, some have argued that this time endpoint is arbitrary, and thus TIA should be defined based on a biologic endpoint (presence or absence of infarcted tissue on brain imaging).
- Symptoms are transient with a TIA because reperfusion occurs, either because of collateral circulation or because of the breaking up of an embolus.

b. **The blockage in blood flow does not last long enough to cause permanent infarction.**

c. **Once a patient has a TIA, there is a high risk of stroke.** The risk is increased within days of the TIA; the risk of stroke at 30 days and 5 years is ∼10% and 30%, respectively.

d. Evaluation after TIA: brain and neurovascular imaging, ECG and cardiac monitoring (inpatient telemetry if admitted, plus ambulatory monitoring for several weeks after), echocardiogram, and labs (CBC, chemistry, lipids, diabetes screening, and others depending on history and risk factors).

Quick HIT

The ABCD^2 score is often used as a risk stratification tool to identify patients at highest risk of early stroke (validated to predict stroke risk within 2 days) that require emergency assessment.

- Age
- Blood pressure elevation shortly after TIA
- Clinical features of stroke
- Duration of TIA symptoms
- Diabetes

4. Risk factors

a. The most important risk factors are **age** and **HTN.** Others include smoking, DM, hyperlipidemia, atrial fibrillation, coronary artery disease (CAD), family history of stroke, previous stroke/TIA, and high-risk lesions on brain imaging.

b. In younger patients, risk factors include oral contraceptive use, hypercoagulable states (e.g., protein C and S deficiencies, antiphospholipid antibody syndrome), vasoconstrictive drug use

(e.g., cocaine, amphetamines), polycythemia vera, and sickle cell disease.

Quick HIT

Remember these causes of stroke:

- Ischemia due to atherosclerosis
- Embolic (e.g., atrial fibrillation with cardioembolism, septic emboli from endocarditis)
- Systemic hypoperfusion (e.g., septic shock)

B. Causes (Figure 5-1)

1. Emboli are a common cause of TIA/CVA. Possible origins of an embolus include:
   a. **Heart** (most common): typically in the setting of atrial fibrillation
   b. Internal carotid artery
   c. Aorta
   d. Paradoxical: Emboli arise from blood clots in the peripheral veins, pass through septal defects (atrial septal defect, a patent foramen ovale, or a pulmonary AV fistula), and reach the brain

CLINICAL PEARL 5-1

TIAs Can Involve Either the Carotid or the Vertebrobasilar System

Carotid System

- Temporary loss of speech; paralysis or paresthesias of contralateral extremity; clumsiness of one limb
- **Amaurosis fugax** (an example of a TIA): transient, curtain-like loss of sight in ipsilateral eye due to microemboli to the retina

Vertebrobasilar System (i.e., Vertebrobasilar TIAs)

- Decreased perfusion of the posterior fossa
- Dizziness, double vision, vertigo, numbness of ipsilateral face and contralateral limbs, dysarthria, hoarseness, dysphagia, projectile vomiting, headaches, and drop attacks

Quick HIT

The source of an embolic stroke is evaluated by:
1. Echocardiogram
1. Vascular imaging (e.g., carotid ultrasound, CTA head/neck)
1. ECG, ambulatory cardiac monitoring

2. Thrombotic stroke—Atherosclerotic plaques may be in the large arteries of the neck (carotid artery disease, which most commonly involves the bifurcation of the common carotid artery), or in medium-sized arteries in the brain (especially the middle cerebral artery [MCA])
3. Lacunar stroke—**small vessel** thrombotic disease
   a. Causes approximately 20% of all strokes; usually affects subcortical structures (basal ganglia, thalamus, internal capsule, brainstem) and not the cerebral cortex
   b. Predisposing factor: A history of **HTN** is present in 80% to 90% of lacunar infarctions. Diabetes is another important risk factor
   c. Narrowing of the arterial lumen is due to **thickening of vessel wall** (not by thrombosis)

d. The arteries affected include small branches of the MCA, the arteries that make up the circle of Willis, and the basilar and vertebral arteries (see Clinical Pearl 5-2)

e. When these small vessels occlude, small infarcts result; when they heal, they are called lacunes

4. Nonvascular causes—Examples include low cardiac output and anoxia (may cause global ischemia and infarction)

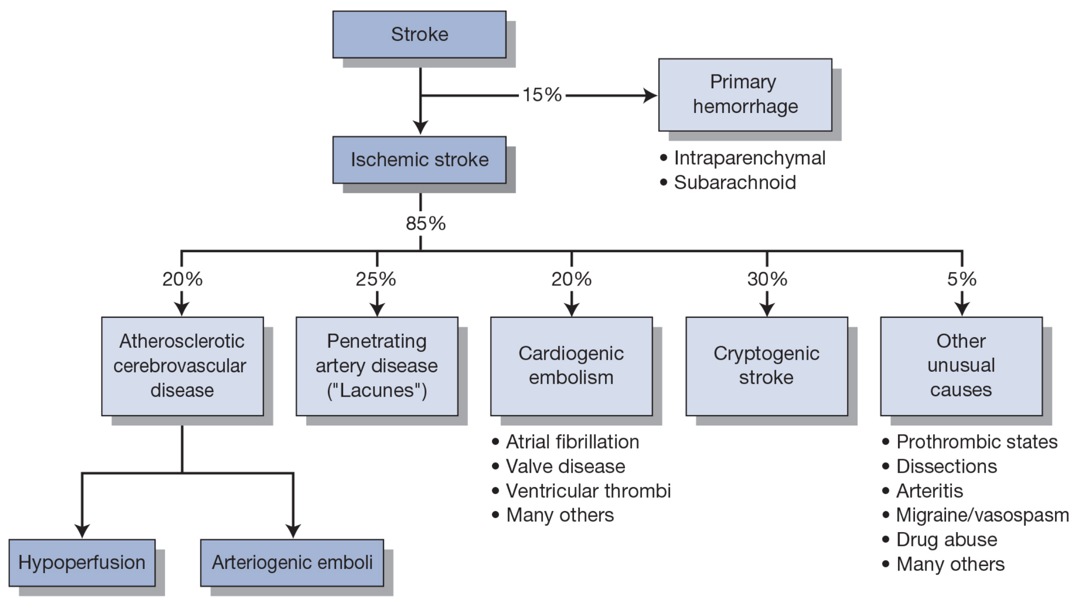


FIGURE 5-1 **Etiology of stroke.**
(Redrawn with permission from Verstraete M, Fuster V, Topol EJ, eds. *Cardiovascular Thrombosis: Thrombocardiology and Thromboneurology*. 2nd ed. Lippincott-Raven; 1998:586. Figure 34-2.)

CLINICAL PEARL 5-2

Subclavian Steal Syndrome

- Caused by stenosis of subclavian artery proximal to origin of vertebral artery—exercise of left arm causes reversal of blood flow down the ipsilateral vertebral artery to fill the subclavian artery distal to the stenosis because it cannot supply adequate blood to left arm
- Leads to decreased cerebral blood flow (blood "stolen" from basilar system)
- Causes symptoms of vertebrobasilar arterial insufficiency (see Clinical Pearl 5-1)
- BP in left arm is less than in right arm; decrease in pulse in left arm
- Upper extremity claudication
- Treatment: surgical bypass

C. Clinical Features

1. Thrombotic stroke—The onset of symptoms may be rapid or stepwise. **Often the patient awakens from sleep with the neurologic deficits** (see Table 5-1)
2. Embolic stroke
   a. The onset of symptoms is **very rapid** (within seconds), and deficits are maximal initially.
   b. Clinical features depend on the artery that is occluded. The MCA is most commonly affected, and neurologic deficits seen in MCA involvement include:
      - Contralateral hemiparesis and hemisensory loss
      - Aphasia (if dominant hemisphere is involved)—for 90% of population this is left cerebral dominance
      - Apraxia, contralateral body neglect, confusion (if nondominant hemisphere is involved)
3. Lacunar stroke—Clinical features are focal and usually contralateral pure motor or pure sensory deficits. Lacunar stroke includes four major syndromes:
   a. Pure **motor** lacunar stroke—if lesion involves the **internal capsule**
   b. Pure **sensory** lacunar stroke—if lesion involves the **thalamus**
   c. Ataxic hemiparesis—incoordination ipsilaterally
   d. Clumsy hand dysarthria

Quick HIT

A carotid bruit has two causes:

- Murmur referred from the heart
- Turbulence in the internal carotid artery (usually atherosclerosis)

Quick HIT

Most common location involves the MCA—results in contralateral weakness, sensory loss, and hyperreflexia.

Quick HIT

Uses of CT Scan of the Head in the ED

- To differentiate ischemic from hemorrhagic infarction
- Identifies 95% of SAHs (and all bleeds >1 cm)
- Identifies abscess, tumor
- Identifies subdural or epidural hematoma

D. Initial Assessment

1. History and neurologic examination (including the National Institutes of Health Stroke Scale, NIHSS). The NIHSS score on admission predicts stroke outcomes.

TABLE 5-1 Deficits Seen in Stroke

Distribution	Location and/or Type of Deficiency
Anterior cerebral artery	Contralateral lower extremity and face
Middle cerebral artery	Aphasia, contralateral hemiparesis
Vertebral/basilar	Ipsilateral: ataxia, diplopia, dysphagia, dysarthria, and vertigo Contralateral: homonymous hemianopsia with basilar—PCA lesions
Lacunar	
Internal capsule	Pure motor hemiparesis
Pons	Dysarthria, clumsy hand
Thalamus	Pure sensory deficit

PCA, posterior cerebral artery.

2. Brain imaging (CT or MRI)
   a. CT scan of the head without contrast is preferred at most centers due to availability and time constraints, and it differentiates an ischemic from a hemorrhagic infarction. Ischemic strokes appear as dark areas on the CT scan (hemorrhagic strokes appear white). It may take 24 to 48 hours to visualize an infarct on CT.
   b. MRI of the brain is more sensitive than CT; it identifies all infarcts, and does so earlier than CT scan. Ninety-five percent of infarcts identified on MRI within 24 hours.
   c. The brain imaging modality can be combined with neurovascular imaging at some centers (e.g., CT with CTA, MRI with MRA).
3. ECG—acute MI or atrial fibrillation may be the cause of embolic strokes.
4. Labs: blood glucose, CBC, electrolytes, creatinine, coags, cardiac enzymes, and others based on patient factors.

Quick HIT

If a young patient (<50) presents with stroke, look for vasculitis, hypercoagulable state, and thrombophilia. Consider the following:

- Protein C, Protein S, antiphospholipid antibodies
- Factor V Leiden mutation
- ANA, ESR, rheumatoid factor
- VDRL/RPR, Lyme serology
- Transesophageal echocardiogram (TEE)

E. Complications

1. Progression of neurologic insult
2. Cerebral edema occurs within 1 to 2 days and can cause **mass effects** for up to 10 days. Hyperventilation and mannitol may be needed to lower intracranial pressure (ICP)
3. Hemorrhage into the infarction—rare
4. Seizures—fewer than 5% of patients

F. Treatment

1. Acute—Supportive treatment (airway protection, oxygen, IV fluids) is initiated. Early recognition of the cause of stroke is unreliable, and early treatment is critical. Therefore, choose therapies that have broad efficacy and safety.
   a. Thrombolytic therapy (t-PA)
      - If administered **within 4.5 hours** of the onset of an acute ischemic stroke, improved clinical outcome is seen at 3 months. Some studies have shown a benefit outside this window, based mostly on brain imaging results.
      - Do not give t-PA if the time of stroke is unknown, if more than 4.5 hours have passed, or if the patient has any of the following: uncontrolled HTN, bleeding disorder, is taking anticoagulants or has a history of recent trauma or surgery. These patients are at increased risk for hemorrhagic transformation.
      - If t-PA is given, there is risk of **intracranial hemorrhage.** Therefore, do not give aspirin for the first 24 hours, perform frequent neurologic checks (every hour), and carefully monitor BP. (Keep BP <185/110 mmHg.)

b. In eligible patients with large artery occlusion who present within 24 hours, endovascular thrombectomy whether or not a thrombolytic has been given.
c. Aspirin should be given as early as possible (unless t-PA is used), and ideally within 48 hours of stroke onset.
d. Anticoagulants (e.g., heparin) **have not been proven to have efficacy in acute stroke.** However, DVT/VTE prophylaxis should be given during hospitalization.
e. Assess the patient's ability to protect their airway, keep NPO, protect against hypo- or hyperglycemia, avoid fever, and elevate the head of the bed 30 degrees to prevent aspiration.

Quick HIT

If stroke is caused by emboli from a cardiac source, anticoagulation is the treatment.

2. BP control—In general, do not give antihypertensive agents in the first 24 hours unless one of the following three conditions is present:
   a. The patient's BP is very high (systolic >220, diastolic >120, or mean arterial pressure >130 mmHg).
   b. The patient has a significant medical indication for antihypertensive therapy. Examples include:
      - Acute MI
      - Aortic dissection
      - Severe heart failure
      - Hypertensive encephalopathy
   c. The patient is receiving t-PA—aggressive blood pressure control is necessary to reduce the likelihood of bleeding.
3. Prevention of stroke recurrence
   a. Lifestyle and pharmacotherapy for risk factors (HTN, DM, smoking, hyperlipidemia, obesity).
   b. Long-term antiplatelet therapy (e.g., aspirin)
   c. High-intensity statin
   d. Anticoagulation for cardioembolic strokes
   e. Surgery for strokes due to carotid artery disease (Figure 5-2)

- **Symptomatic patients**—three major studies have established the benefit of carotid endarterectomy in symptomatic patients with carotid artery stenosis of >**70%**. (The NASCET trial was the most influential)
- **Asymptomatic patients**—four major studies have investigated the benefit of carotid endarterectomy in asymptomatic patients. Three found no benefit. One study (ACAS) found that in asymptomatic patients who have a carotid artery stenosis of >60%, the benefits of surgery are very small. **Therefore, in asymptomatic patients, reduction of atherosclerotic risk factors and use of aspirin are recommended**

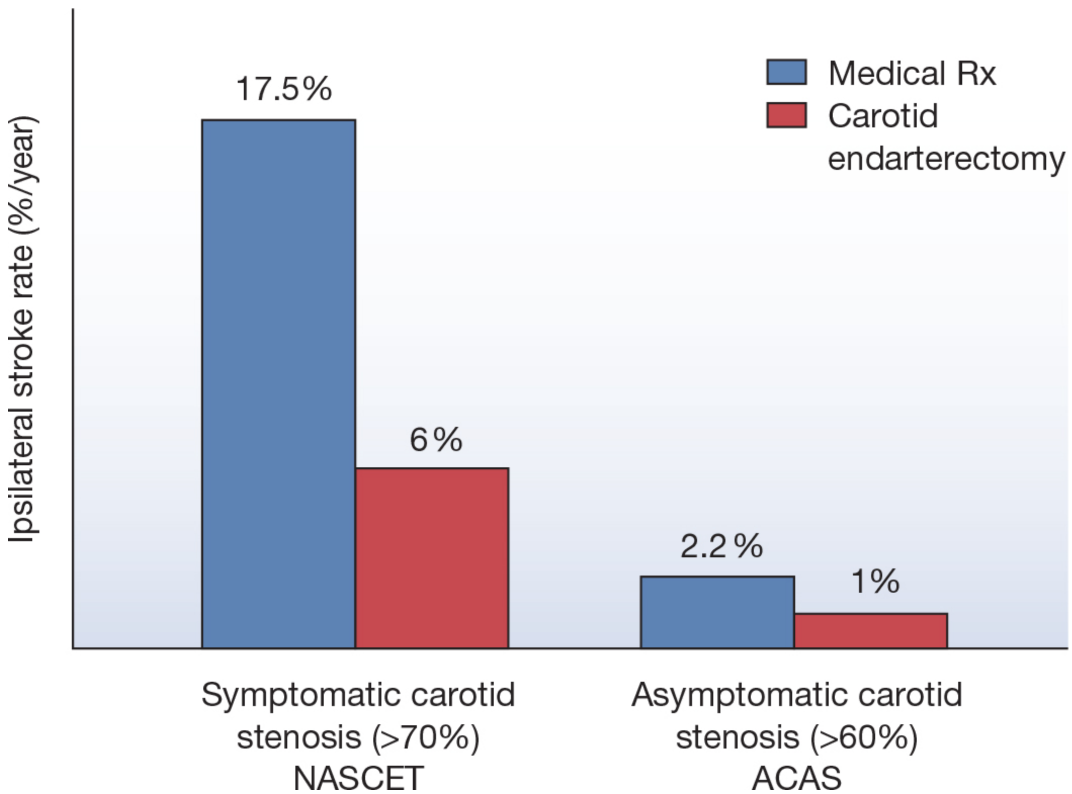


FIGURE 5-2 **Effect of carotid endarterectomy in carotid stenosis. NASCET, North American Symptomatic Carotid Endarterectomy Trial; ACAS, asymptomatic carotid atherosclerosis study.**
(Redrawn with permission from Verstraete M, Fuster V, Topol EJ, eds. *Cardiovascular Thrombosis: Thrombocardiology and Thromboneurology*. 2nd ed. Lippincott-Raven; 1998:590. Figure 34-4.)

Quick HIT

If carotid stenosis is >70% and patient is symptomatic, carotid endarterectomy is indicated.

Hemorrhagic Stroke

A. Intracerebral Hemorrhage

1. **General characteristics**
   a. ICH is associated with a high mortality rate (50% at 30 days). For those who survive, there is significant morbidity.
   b. Hematoma formation and enlargement may lead to local injury and increase in intracerebral pressure.

Quick HIT

Two major categories of hemorrhagic stroke:
- ICH—bleeding into brain parenchyma
- SAH—bleeding into the CSF; outside brain parenchyma

2. **Causes**
   a. HTN **(particularly a sudden increase in BP)** is the most common cause (50% to 60% of cases).
      - HTN causes a rupture of small vessels deep within the brain parenchyma. Chronic HTN causes degeneration of small arteries, leading to microaneurysms, which can rupture easily.
      - It is typically seen in older patients; risk increases with age.
   b. Ischemic stroke may convert to a hemorrhagic stroke.
   c. Other causes include amyloid angiopathy (10%), anticoagulant or thrombolytic use (10%), brain tumors (5%), and AV malformations (5%).

Quick HIT

Cocaine is one of the main causes of stroke in young patients. ICH, ischemic stroke, and SAH are all associated with cocaine use.

3. **Locations**
   a. Basal ganglia (66%)
   b. Pons (10%)
   c. Cerebellum (10%)
   d. Other cortical areas

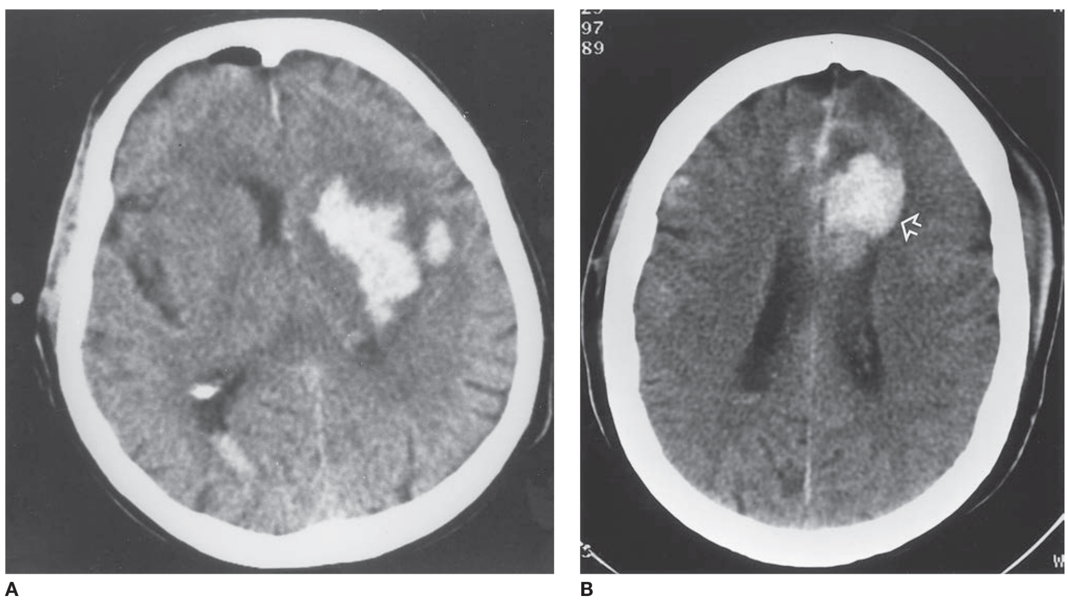


FIGURE 5-3 **A: Spontaneous ICH hemorrhage in a hypertensive patient. B: On CT scan, ischemic stroke appears dark, whereas hemorrhagic stroke appears white.**
(**A** reprinted with permission from Daffner RH, ed. *Clinical Radiology: The Essentials*. 2nd ed. Lippincott Williams & Wilkins; 1999:526. Figure 12.37A. **B** reprinted with permission from Daffner RH, ed. *Clinical Radiology: The Essentials*. 2nd ed. Lippincott Williams & Wilkins; 1999:528. Figure 12.40B.)

Quick HIT

Pupillary findings in ICH often correspond to brainstem involvement

4. **Clinical features**
   a. Abrupt onset of a focal neurologic deficit that worsens steadily over 30 to 90 minutes
   b. Altered level of consciousness, stupor, or coma
   c. Headache, vomiting
   d. Signs of increased ICP
5. **Diagnosis**
   a. CT scan of the head diagnoses 95% of ICH (may miss very small bleeds) (Figure 5-3)
   b. Coagulation panel and platelets—check these to evaluate for bleeding diathesis
6. **Complications**
   a. Increased ICP
   b. Seizures
   c. Rebleeding
   d. Vasospasm
   e. Hydrocephalus
   f. SIADH
7. **Treatment**
   a. Admission to the ICU
   b. ABCs (airway, breathing, and circulation)—airway management is important due to altered mental status and decreased respiratory drive. Patients often require intubation.
   c. BP reduction
      - Elevated BP increases ICP and can cause further bleeding. However, hypotension can lower cerebral blood flow, worsening the neurologic deficits. Therefore, **BP reduction must be gradual.**
      - If SBP >220 mmHg, immediate lowering usually with IV agents to below this level. Then gradual reduction over 1 to 2 hours to SBP 140 to 160 mmHg. Common IV agents used include nicardipine, labetalol, nitroprusside, and others.
   d. Initial management of elevated ICP includes elevating the head of the bed to 30 degrees and appropriate sedation and pain control. Mannitol (osmotic agent) is often used to lower ICP; other options include hyperventilation, barbiturates, neuromuscular blockade, and CSF drainage.

e. If the patient is on anticoagulation or an antiplatelet agent, reversal agents (vitamin K for warfarin, protamine sulfate for heparin, prothrombin complex concentrate for warfarin and the newer oral anticoagulants, etc.).
f. Use of steroids is harmful and is **not** recommended.
g. Rapid surgical evacuation of **cerebellar** hematomas can be lifesaving. However, surgery is **not** helpful in most cases of ICH.

***Quick* HIT**

Common Sites of SAH

- Junction of anterior communicating artery with anterior cerebral artery
- Junction of posterior communicating artery with the internal carotid artery
- Bifurcation of the MCA

***Quick* HIT**

Polycystic kidney disease is associated with berry aneurysms.

***Quick* HIT**

If SAH suspected, first perform CT head. If negative, and there is still suspicion, then perform lumbar puncture.

B. Subarachnoid Hemorrhage

1. **General characteristics**
   a. Mortality rate can be as high as 30% to 50% at 30 days.
   b. Locations—Saccular (berry) aneurysms occur at bifurcations of arteries of the circle of Willis.
2. **Causes**
   a. Ruptured saccular (berry) aneurysms are the most common cause—has higher morbidity and mortality than other causes.
   b. Trauma is also a common cause.
   c. AV malformation.

3. **Clinical features**
   a. Sudden, severe **(often excruciating)** headache in the absence of focal neurologic symptoms; classic description is **“the worst headache of my life”** but may also be more subtle.
   b. Sudden, transient loss of consciousness—in approximately 50% of patients.
   c. Vomiting (common).
   d. Meningeal irritation, nuchal rigidity, and photophobia—can take several hours to develop.
   e. Death—25% to 50% of patients die with the first rupture. Those who survive will recover consciousness within minutes.
   f. Retinal hemorrhages—in up to 30% of patients.
4. **Diagnosis**
   a. Noncontrast CT scan—identifies the majority of subarachnoid hemorrhages (SAHs). However, CT scan may be negative in up to 10% of cases.
   b. **Perform lumbar puncture (LP) if the CT scan is unrevealing or negative and clinical suspicion is high. LP is diagnostic.**
      - **Blood in the CSF** is a hallmark of SAH. (Be certain that it is not blood from a traumatic spinal tap.)
      - **Xanthochromia** (yellow color of the CSF) is the gold standard for diagnosis of SAH. Xanthochromia results from RBC lysis. Xanthochromia implies that blood has been in CSF for several hours and that it is not due to a traumatic tap.
   c. Once SAH is diagnosed, order a cerebral angiogram. It is the definitive study for detecting the site of bleeding (for surgical clipping).
5. **Complications**
   a. Re-rupture—occurs in up to 30% of patients.
   b. Vasospasm—occurs in up to 50% of patients (more often with aneurysmal SAH); can cause ischemia/infarction and therefore stroke.
   c. Hydrocephalus (communicating)—secondary to blood within the subarachnoid space hindering normal CSF flow.
   d. Seizures may occur (blood acts as an irritant).
   e. SIADH

6. **Treatment**
   a. Endovascular coiling or surgical clipping are the most common treatments of aneurysms.
   b. Medical—therapy reduces the risks of rebleeding and cerebral vasospasm.
      - Blood pressure control, targeting SBP <160 or MAP <110.
      - Reverse effects of anticoagulants.
      - DVT/VTE prophylaxis (while holding other antithrombic and anticoagulant medications).
      - Other supportive measures including analgesia for headache, stool softeners to avoid straining, IV fluids as needed to maintain euvolemia.
      - Calcium channel blocker (nimodipine) for vasospasm—lowers the incidence of cerebral infarction by one-third.

A 37-year-old woman presents with a severely intense headache that began a few hours ago. The headache has not improved since then and the patient has vomited several times. She reports that it is diffusely painful, and she is unable to recall if any "funny sensations" occurred prior to the headache. She does not report head trauma or fever. A noncontrast CT scan of the head shows a small amount of blood in the basal cisterns.

Which of the following is the underlying cause of this patient's headache?

A. Venous sinus thrombosis
B. Ruptured berry aneurysm
C. Arteriovenous malformation
D. Amyloid angiopathy

- **The answer is B: Ruptured berry aneurysm.** This patient is likely suffering from a nontraumatic subarachnoid hemorrhage as evidenced by the CT scan. CT scan findings in a subarachnoid hemorrhage include bright (hyperdense) signals that represent *acute* bleeding (usually in the cisterns). In the case of nontraumatic subarachnoid hemorrhages, the most common cause is ruptured berry or saccular aneurysms. Rupture is more likely for aneurysms greater than 7 mm. Of note, if this patient presented with a negative head CT and a subarachnoid hemorrhage was still suspected, the next best step is to perform a lumbar puncture, which will demonstrate xanthochromia. **(A)** Venous sinus thrombosis typically presents with *progressively* worsening headache and causes hemorrhage along the major cerebral draining veins. **(C)** Arteriovenous malformation is also a cause of subarachnoid hemorrhages (and intracerebral hemorrhages), but the most common cause of nontraumatic subarachnoid hemorrhages is a ruptured aneurysm. **(D)** Amyloid angiopathy is the second most common cause of intracerebral hemorrhage. However, this type of

hemorrhage is *lobar* in its location and results from abnormal β-pleated amyloid protein deposition in the cerebral blood vessels.

Seizures

A. General Characteristics

1. A seizure occurs when there is a sudden abnormal discharge of electrical activity in the brain (see Clinical Pearl 5-3).
2. Epilepsy refers to a brain disorder that causes a predisposition to recurrent seizures.

B. Causes (four M's, four I's)

1. **M**etabolic and electrolyte disturbances—hyponatremia, hypoglycemia or hyperglycemia, hypocalcemia, uremia, thyroid storm, hyperthermia
2. **M**ass lesions—brain metastases, primary brain tumors, hemorrhage

CLINICAL PEARL 5-3

Important Aspects of H & P in a Patient Presenting With a Seizure

- Acquire a description of the seizure from bystanders (e.g., postictal state, loss of continence).
- Determine what is the baseline state for the patient. Is the patient a known epileptic? Look into missed doses of antiepileptics, or any recent change in dosages/medications.
- Examine the patient for any injuries—head or spine, fractures, posterior shoulder dislocation, tongue lacerations, bowel/bladder incontinence.
- Look for signs of increased ICP.
- Perform a complete neurologic examination.

3. **M**issing drugs
   a. **Nonadherence with antiseizure medications** in patients with epilepsy

   b. **Acute withdrawal from alcohol, benzodiazepines, barbiturates**
4. **M**iscellaneous
   a. Pseudoseizures—not true seizures but are psychiatric in origin; are often difficult to distinguish from true seizures without an EEG
   b. Eclampsia—A preeclamptic pregnant woman seizing no longer has preeclampsia! The only definitive treatment for eclampsia is delivery, but a magnesium infusion is the pharmacologic treatment of choice
   c. Hypertensive encephalopathy—severe hypertension can cause cerebral edema
5. **I**ntoxications—cocaine, lithium, lidocaine, theophylline, metal poisoning (e.g., mercury, lead), carbon monoxide poisoning
6. **I**nfections—septic shock, bacterial or viral meningitis, brain abscess
7. **I**schemia—stroke, TIA (common cause of seizure in elderly patients)
8. **I**ncreased ICP—for example, due to trauma

A 36-year-old woman presents with a 2-day history of fever, stiff neck, and headaches. She also was reported to have had one seizure just prior to her admission. The patient has a temperature of 39°C, blood pressure of 120/80 mmHg, and heart rate of 106 beats per minute. A lumbar puncture is performed and her CSF studies reveal the following.

Opening pressure	218 mm H_2O (normal)
Protein	210 mg/dL (high)
Glucose	58 mg/dL (normal)
Leukocytes	160/mm^3 (high)
Lymphocytes	92%
Neutrophils	8%
RBC	220/mm^3 (high)

Which of the following is the most likely diagnosis in this patient?

A. Meningococcal meningitis
B. Herpes simplex encephalitis
C. Tuberculous meningitis
D. Pneumococcal meningitis

- **The answer is B: Herpes simplex encephalitis.** The patient in this question likely has herpes simplex (HSV) encephalitis, which accounts for almost 20% of viral encephalitis cases and presents with fever, focal seizures, and sometimes aphasia, ataxia, hemiparesis, and behavioral symptoms. HSV encephalitis typically affects the temporal lobes of the brain and has an acute onset. CSF studies reveal lymphocytosis, elevated protein levels, normal glucose levels, and occasionally increased levels of RBCs due to hemorrhagic destruction of the temporal lobes. **(A, D)** Bacterial meningitis will present with *low* glucose in the CSF. In addition, rather than lymphocytosis, increased neutrophils will be seen on CSF analysis.

(C) Fungal meningitis often presents with *low* glucose such as bacterial meningitis, but will accompany a lymphocytosis. The patient in this question has a CSF analysis that is consistent with a viral etiology.

Quick HIT

Partial seizures may evolve into generalized seizures. When this happens, it is called **secondary generalization.**

Quick HIT

It is important (although sometimes difficult) to differentiate between absence (petit mal) and complex partial seizures because their treatments are different. Also, absence seizures disappear in adulthood, whereas complex partial seizures do not.

C. Types of Seizures

1. Partial seizure—accounts for 70% of patients with epilepsy older than 18 years of age (Figure 5-4). It begins in one part of the brain (typically the temporal lobe) and initially produces symptoms related to the region of the cortex involved
   a. Simple partial seizure
      - **Consciousness remains intact.** The seizure remains localized but may evolve into a complex partial seizure
      - May involve transient unilateral clonic–tonic movement
   b. Complex partial seizure
      - **Consciousness is impaired;** postictal confusion
      - Automatisms (last 1 to 3 minutes)—purposeless, involuntary, repetitive movements (such as lip smacking or chewing); patients may become aggressive if restraint is attempted
      - Olfactory or gustatory hallucinations

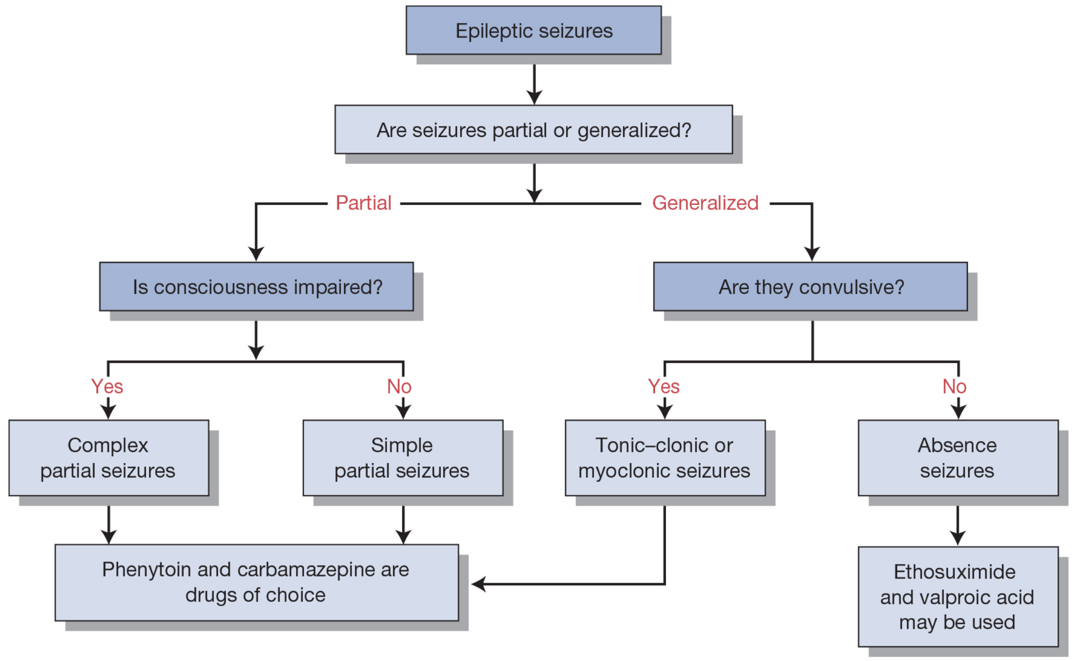


FIGURE 5-4 **Epileptic seizure flowchart.**
(Adapted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:2866. Figure 426.1.)

2. Generalized seizure—characterized by **loss of consciousness.** Involves disruption of electrical activity in the entire brain.
   a. Tonic–clonic (grand mal) seizure—bilaterally symmetric and without focal onset.
      - Begins with sudden loss of consciousness—a fall to the ground.
      - Tonic phase—The patient becomes rigid; trunk and limb extension occurs. The patient may become apneic during this phase.
      - Clonic phase—This is musculature jerking of the limbs and body for at least 30 seconds.
      - The patient then becomes flaccid and comatose before regaining consciousness.
      - Postictal confusion and drowsiness are characteristic and can last for hours, although 10 to 30 minutes is more typical.
      - Other features may include tongue biting, vomiting, apnea, and incontinence (urine and/or feces).
   b. Absence (petit mal) seizure.

- Typically involves school-aged children—usually resolves as child grows older.
- Patient seems to disengage from current activity and “stare into space”—then returns to the activity several seconds later; patient looks “absent minded” during these episodes, which are often confused with “daydreaming.”
- Episodes are brief (lasting a few seconds) but may be quite frequent (up to 100 times per day).
- Impairment of consciousness but **no** loss of postural tone or continence, and no postictal confusion.
- Minor clonic activity (eye blinks or head nodding) in up to 45% of cases.

D. Diagnosis

1. If the patient has a known seizure disorder (epileptic), check drug levels of their antiseizure medications to ensure they are in the therapeutic range.
2. If the patient history is unclear or if this is the patient’s first seizure:
   a. CBC, electrolytes, blood glucose, LFTs, renal function tests, serum calcium, urinalysis.
   b. EEG
      - Although the EEG is the most helpful diagnostic test in the diagnosis of a seizure disorder, an abnormal EEG pattern alone is not adequate for the diagnosis of seizures.
      - A normal EEG in a patient with a first seizure is associated with a lower risk of recurrence.
   c. CT scan of the head—to identify a structural lesion
   d. MRI of the brain—with and without gadolinium (first without)
      - An important part of the workup of a patient with a first seizure.
      - **More sensitive than a CT scan** in identifying structural changes, but not always practical.
   e. LP and blood cultures—if patient is febrile

Quick HIT

Laboratory Values to Check Immediately in a Patient With a Seizure

- Serum calcium
- Serum sodium
- Serum glucose or Accu-Chek
- BUN

E. Treatment

1. General principles
   a. For all seizures, ABCs take priority: Secure airway and roll patient onto his side to prevent aspiration.
   b. Patients with a history of seizures (epilepsy).
      - Assess for missed doses of medications, new insults or medications that would precipitate seizures, and so on.
      - These patients should be chronically managed by a neurologist. Treatment with one of the standard antiepileptic drugs provides adequate control in roughly half of adult patients.
   c. Patient with a first seizure.
      - Antiseizure medications—weigh risks and benefits of treatment and the risk of recurrence before initiating.
      - Antiseizure medication is started if the patient has had two or more unprovoked seizures, or they are at a high risk of recurrence.
2. Antiseizure medications
   a. No single agent is recommended as first line treatment. This depends on the seizure type, medical comorbidities and other medications the patient is taking (noting drug–drug interactions are frequent with these medications).

Quick HIT

Status Epilepticus

- Refers to prolonged, sustained unconsciousness with persistent convulsive activity in a seizing patient. Typically suspected after 5 minutes of seizure activity, with a significant risk of long-term complications after 30 minutes of seizure activity.
- A medical emergency, with a mortality rate of up to 20%.
- Management involves establishing an airway, and **giving an IV benzodiazepine (if IV access is achieved; typically diazepam or lorazepam), and an** IV antiseizure medication.

Quick HIT

Remember that many antiseizure medications are teratogenic. (Do a pregnancy test before prescribing!)

Movement Disorders

Parkinson Disease

A. General Characteristics

1. Parkinson disease is the most common hypokinetic movement disorder.
2. Onset is usually after age 50 years.
3. Parkinson disease is essentially a clinical diagnosis. Laboratory studies play no role in diagnosis.
4. Parkinsonism refers to symptoms and signs of Parkinson disease and can result from many conditions (e.g., medications). Up to 10% of patients with parkinsonism will have "Parkinson-plus syndromes":
   a. Multiple system atrophy: parkinsonism plus one of the following subtypes: dysautonomia (Shy–Drager syndrome), cerebellar ataxia (MSA-C), or dystonia (MSA with predominant parkinsonism).

b. Progressive supranuclear palsy: parkinsonism plus prominent oculomotor deficits.
c. Corticobasal degeneration: parkinsonism (usually asymmetric) plus impaired cognition, dystonia, sensory deficits, and myoclonus.

Quick HIT

The basal ganglia/striatal region normally operates as a balanced system comprising the dopaminergic system and the cholinergic system. In Parkinson disease, the dopaminergic pathway is compromised, and the cholinergic system operates unopposed. Therefore, the goal of treatment is either to enhance dopamine's influence or to inhibit acetylcholine's influence.

B. Clinical Features

1. Pill-rolling tremor at rest (worsens with emotional stress) (see Clinical Pearl 5-4). Tremor goes away when performing routine tasks
2. Bradykinesia—slowness of voluntary movements
3. Rigidity is characteristic. "Cogwheel rigidity" refers to a ratchet-like jerking, which can be elicited by testing the tone in one limb while the patient clenches the opposite fist

Quick HIT

Lewy bodies (hyaline inclusion bodies) are a key neuronal finding in the brains of patients with Parkinson disease.

CLINICAL PEARL 5-4

Progressive Supranuclear Palsy (PSP)

- PSP is a degenerative condition of the brainstem, basal ganglia, and cerebellum, most commonly affecting middle-aged and elderly men.
- Like Parkinson disease, PSP causes bradykinesia, limb rigidity, cognitive decline, and follows a progressive course.
- Unlike Parkinson disease, PSP
  - Does **not cause tremor**
  - Does cause ophthalmoplegia

4. Poor postural reflexes; difficulty initiating the first step, and walking with small shuffling steps; stooped posture
5. Masked (expressionless) facies; decreased blinking
6. Dysarthria and dysphagia, micrographia (small handwriting)
7. Impairment of cognitive function (dementia) in advanced disease
8. Autonomic dysfunction can lead to orthostatic hypotension, constipation, increased sweating, and oily skin
9. Personality changes present in early stages. Patients become withdrawn, apathetic, and dependent on others. Depression is common and can be significant—causes worsening of parkinsonian symptoms
10. Follows progressive course—significant disability usually presents within 5 to 10 years; indirectly leads to increased mortality

Quick HIT

The clinical features of Parkinson disease can be remembered with the mnemonic TRAP: Tremor, Rigidity, Akinesia, Postural instability.

C. Treatment

1. No cure—goals are to delay disease progression and relieve symptoms.
2. First-line treatments include levodopa, monoamine oxidase inhibitors (MAOIs), dopamine agonists, and amantadine. Initial treatment choice depends on the severity of symptoms.

3. Levodopa is a dopamine precursor that is often used for more severe symptoms.
   a. Carbidopa is a decarboxylase inhibitor added to levodopa to prevent peripheral conversion of levodopa into dopamine before it crosses the blood–brain barrier.
   b. It is the most effective of all the antiparkinsonian drugs.
   c. Side effects
      - Dyskinesias (involuntary, often choreic movements) can occur after 5 to 7 years of therapy. This is a major concern, and may warrant delay in initiating carbidopa-levodopa for as long as possible.
      - Nausea/vomiting, anorexia, HTN, hallucinations.
   d. Levodopa does show an "on–off" phenomenon (over the course of the day) during treatment, which leads to fluctuations in symptoms. This is due to dose–response relationships. It often occurs in advanced disease.

Quick HIT

Medications That Cause Parkinsonian Side Effects

- Neuroleptic drugs (chlorpromazine, haloperidol, perphenazine)
- Metoclopramide
- Reserpine

Quick HIT

Patients with tremor as a major symptom of Parkinson disease have a better prognosis than those who have bradykinesia as a predominant finding.

4. Dopamine-receptor agonists (ropinirole, pramipexole, rotigotine are nonergot dopamine agonists).
   a. May control symptoms and delay need for levodopa for several years.
   b. The ergot-derived dopamine agonists (e.g., bromocriptine, cabergoline) are no longer commonly used.

   c. These can be useful for sudden episodes of hesitancy or immobility (described as "freezing").
5. Monoamine oxidase inhibitors
   a. Include selegiline, rasagiline, safinamide
   b. They work to inhibit monoamine oxidase B activity (increases dopamine activity) and reduces metabolism of levodopa.
   c. Often used with mild symptoms or as an adjunct.
6. Amantadine (antiviral agent)—mild benefit, mostly for early or mild disease.
7. Anticholinergic drugs can be used to help with tremor (e.g., benztropine). Other Parkinson symptoms (depression, anxiety, psychosis, excessive daytime sleepiness, etc.) should be screened for and treated if present.
8. Other options that require a device: continuous levodopa-carbidopa intestinal gel infusion, continuous apomorphine (dopamine agonist) infusion.
9. Surgery (deep brain stimulation)—if patient does not respond to medications or in patients who develop severe disease before age 40 years.

Huntington Chorea

A. General Characteristics

1. **Autosomal dominant**, so lack of family history makes this diagnosis unlikely.
2. Onset is between 30 and 50 years of age. Symptoms worsen steadily, with 15 years being the typical duration from onset to death.
3. It is caused by a mutation on chromosome 4 (expanded triplet repeat sequence)—CAG leads to a loss of GABA-producing neurons in the striatum.

B. Clinical Features

1. Chorea—involving the face, head and neck, tongue, trunk, and extremities.
2. Altered behavior—irritability, personality changes, antisocial behavior, depression, obsessive-compulsive features, and/or psychosis.

3. Impaired mentation—progressive dementia is a key feature; 90% of patients are demented before age 50 years.
4. Gait is unsteady and irregular. Ultimately bradykinesia and rigidity prevail.
5. Incontinence.

> **Quick HIT**
>
> Always keep Wilson disease in mind in a **young patient** with movement disorders (see Chapter 3).

C. Diagnosis

1. MRI shows atrophy of the head of caudate nuclei.
2. DNA testing confirms the diagnosis. Genetic counseling plays an important role.

D. Treatment

Treatment is symptomatic—there is no curative treatment. Dopamine blockers may help with the psychosis and improve chorea. Anxiolytic and antidepressant therapy may be necessary.

Tremor

A. Physiologic Tremor

1. **Causes** (see Table 5-2)
   a. Fear, anxiety, fatigue
   b. Metabolic causes: hypoglycemia, hyperthyroidism, pheochromocytoma
   c. Toxic causes (e.g., alcohol withdrawal, valproic acid, lithium, methylxanthines—caffeine and theophylline)
2. **Treatment:** Treat the underlying cause, if known; otherwise, no treatment is necessary

TABLE 5-2 **Common Tremors and Associated Features**

Feature	Parkinsonian	Cerebellar	Essential
Characteristic Setting	Rest	With action—"intention tremor"	With certain postures (e.g., arms outstretched) or certain tasks (e.g., handwriting)
Description	Pill-rolling	Coarse	Fine
Etiology	Idiopathic or adverse effect of neuroleptic	Multiple possible etiologies	Often familiar
Associated Features	Rigidity, bradykinesia, shuffling gait	Ataxia, nystagmus, dysarthria	Head tremor, vocal tremulousness
Improved By	Action	Rest (no tremor at rest)	Alcohol

***Quick* HIT**

There is no known association between essential tremor and Parkinson disease.

B. Essential Tremor

1. Common; inherited (autosomal dominant) in up to one-third of patients.
2. It is induced or exacerbated by intentional activity, such as drinking from a cup or use of utensils, and is **markedly decreased by alcohol use**. Screen for alcohol use disorder in these patients.
3. Distorted handwriting is often present. Note that bradykinesia, rigidity, shuffling gait, or postural instability are all absent.
4. Treat with propranolol.

C. Neurologic Diseases

(e.g., Parkinson disease, cerebellar disease, Wilson disease)

Ataxia

A. General Characteristics

1. Gait instability
2. Loss of balance
3. Impaired limb coordination

B. Causes

1. Acquired causes: alcohol intoxication, vitamin B_{12} or thiamine deficiency, cerebellar infarction or neoplasm, demyelinating disease (multiple sclerosis [MS], AIDS), and tertiary syphilis **(tabes dorsalis)**
2. Inherited causes
   a. Friedreich ataxia
      - Autosomal recessive inheritance, onset by young adulthood
      - Presents with ataxia, nystagmus, impaired vibratory sense, and proprioception

   b. Ataxia telangiectasia
      - Autosomal recessive inheritance, childhood onset
      - Symptoms similar to those of Friedreich ataxia plus telangiectases
      - Increased incidence of cancer

C. Treatment

Treat underlying cause if possible.

Restless Leg Syndrome

- A common disorder manifesting as an uncomfortable sensation to move the legs (sometimes the arms as well), that usually occurs during the evening and at rest.
- The pathophysiology is unclear, but it can be associated with iron deficiency and certain medications.
- Treat iron deficiency or withdraw offending medications if possible. If pharmacologic therapy is indicated, then dopamine agonists are typically used (e.g., pramipexole, ropinirole).

Tourette Syndrome

A. General Characteristics

1. Associated with obsessive-compulsive disorder.
2. Onset before age 21 years.
3. Thought to have autosomal dominant inheritance pattern.
4. Not all patients with tics have Tourette syndrome.
5. Not all patients with Tourette syndrome experience coprolalia (involuntary swearing).

Quick HIT

Tics

- Motor tics (e.g., facial grimace, blinking, head jerking, shoulder shrugging)
- Phonic tics (e.g., grunting, sniffing, clearing throat, coprolalia, repetition of words)
- Conditions that must be ruled out include seizures, tardive dyskinesias, and Huntington disease.

B. Clinical Features

(occur frequently and regularly). Must have both motor and phonic tics.

1. Motor tics (multiple)
2. Phonic tics (at least one kind)

C. Treatment

1. Assess and treat comorbid conditions (e.g., ADHD)
2. Behavioral interventions (habit reversal training, comprehensive behavioral intervention for tics)
3. Medication options for debilitating tics include botulinum toxin (for focal tics), tetrabenazine, fluphenazine, aripiprazole, risperidone

Dementia

Overview

A. General Characteristics

1. Dementia is a progressive deterioration of cognitive function, with deficits that interfere with activities of daily living.
2. The most important risk factor for dementia is **increasing age.**

***Quick* HIT**

Mild Cognitive Impairment

- Mild cognitive impairment—an abnormal decline in cognitive dysfunction on the spectrum between normal aging and dementia. It is often a precursor to dementia, although it may be reversible (e.g., pseudodementia from depression).

B. Differential Diagnosis of Dementia

1. Evaluating a patient for a new diagnosis of dementia should focus on ruling out dementia-mimics, as well as trying to establish the dementia subtype.
2. Primary neurologic disorders (see Clinical Pearl 5-5)
   a. Alzheimer disease is often the presumptive diagnosis since it is the most common. If there are vascular risk factors, or features atypical for Alzheimer disease, then other subtypes should be considered.
   b. Vascular dementia, or **multi-infarct dementia,** is a stepwise decline due to a series of cerebral infarctions.
   c. Space-occupying lesions, such as brain tumor or chronic subdural hematoma.
   d. Normal pressure hydrocephalus—triad of dementia, gait disturbance, and urinary incontinence; normal CSF pressure and dilated ventricles.
   e. Dementia with Lewy bodies (see section below).

f. Frontotemporal dementia (Pick disease)—clinically similar to Alzheimer disease.
g. Other neurologic conditions: MS, Parkinson disease, Huntington disease, Wilson disease.

3. Infections
   a. HIV infection (AIDS-related dementia)
   b. Neurosyphilis
   c. Cryptococcal infection of CNS
   d. Creutzfeldt–Jakob disease (spongiform encephalopathy)
   e. Progressive multifocal leukoencephalopathy

CLINICAL PEARL 5-5

Causes of Dementia

Potentially Reversible Causes of Dementia

- Hypothyroidism
- Neurosyphilis
- Vitamin B_{12}/folate deficiency/thiamine deficiency
- Medications
- Normal pressure hydrocephalus
- Depression
- Subdural hematoma

Irreversible Causes of Dementia

- Alzheimer disease
- Parkinson’s, Huntington’s
- Multi-infarct dementia
- Dementia with Lewy bodies, Pick disease
- Unresectable brain mass
- HIV dementia
- Korsakoff syndrome
- Progressive multifocal leukoencephalopathy
- Creutzfeldt–Jakob disease

4. Metabolic disorders
   a. Thyroid disease (hypothyroidism or hyperthyroidism)
   b. Vitamin B_{12} deficiency

   c. Thiamine deficiency—common in patients with alcohol use disorder; if untreated can lead to Korsakoff dementia (irreversible)
   d. Niacin deficiency
5. Drugs and toxins
   a. Substance use disorders
   b. Toxic substances: aniline dyes, metals (e.g., lead)
6. Pseudodementia (depression)—severe depression may cause a decline in cognition that is difficult to distinguish clinically from Alzheimer disease, but is responsive to antidepressant therapy

C. Clinical Approach to Dementia

1. Patient history—Ask patients and their family members about the nature of onset, specific deficits, physical symptoms, and comorbid conditions. Review all medications, as well as family and social history.
2. Physical examination
   a. Focus on a thorough neurologic examination and mental status examination.
   b. Gait analysis often sheds light on movement disorders, mass lesions, and nonpressure hydrocephalus.
3. Laboratory and imaging studies—Consider the following when investigating the cause of dementia: CBC with differential, chemistry panel, thyroid function tests (TSH), vitamin B_{12}, folate level, screening for infectious diseases (e.g., HIV, syphilis), and CT scan or MRI of the head.

D. Treatment and Management

1. Treat reversible causes.
2. Evaluate chronic medication use that could be contributing.
3. Treat/control comorbid medical conditions; for example, diabetes, HTN, depression, visual and hearing impairment.
4. Pharmacologic therapy may be of benefit (see specific diseases below).
5. A multidisciplinary approach includes support groups for caregivers/families of patients with irreversible dementias.

Alzheimer Disease

A. General Characteristics

1. Epidemiology
   a. Alzheimer disease is a very common cause of death in the United States.
   b. Prevalence increases with age—Approximately 10% to 15% of individuals over age 65, and 15% to 30% of individuals over age 80 have Alzheimer disease. However, many will die of other causes first.
2. Risk factors
   a. **Age**
   b. Family history (especially for early-onset Alzheimer disease)
   c. Acquired risk factors (hypertension, diabetes, etc.)
3. The pathogenesis remains unclear, but a heritable component may be present. Genes that affect amyloid in the brain, and APOE e4 allele mutations
4. Pathology (noted at autopsy):
   a. Quantity of senile plaques (age-specific)—focal collections of dilated, tortuous neuritic processes surrounding a central amyloid core (amyloid β-protein)
   b. Quantity of neurofibrillary tangles containing abnormal tau proteins
   c. Neuronal loss and prominent atrophy

Quick HIT

Most important risk factor for Alzheimer disease is age.

Quick HIT

Patients with Alzheimer disease often have **cerebral atrophy** secondary to neuronal loss. Ventricles will correspondingly be enlarged.

B. Clinical Features

1. Begins insidiously but tends to progress at a steady rate.
2. The average time from onset to death is 5 to 10 years (with some variability).
3. Stages
   a. Early stages—mild forgetfulness, impaired ability to learn new material, poor performance at work, poor concentration, changes in personality, impaired judgment (e.g., inappropriate humor).
   b. Intermediate stages—memory is progressively impaired. Patients may be aware of the condition, yet denial is often present. Visuospatial disturbances are common (getting lost in a familiar place and difficulty following directions). Patients may repeat questions over and over.
   c. Later stages—assistance is needed for activities of daily living. Patients have difficulty remembering the names of relatives/friends or major aspects of their lives. Paranoid delusions (e.g., victim of theft) and hallucinations are common.
   d. Advanced disease—complete debilitation and dependence on others, incontinence (bowel/bladder); patient may even forget their own name.
   e. Death is usually secondary to infection or other complications of a debilitated state.

C. Diagnosis

1. Alzheimer disease is primarily a **clinical or presumptive diagnosis.**

D. Treatment

1. Cholinesterase inhibitors—brains of patients with Alzheimer disease have lower levels of acetylcholine. **Avoid anticholinergic medications!** Options include donepezil, rivastigmine, and galantamine.
2. Patients with mild to moderate disease are the most likely to benefit.
3. Memantine is an NMDA antagonist that may be neuroprotective, and is often used for patients with moderate to severe disease.
4. Other treatment options with some data include aducanumab (monoclonal antibody against amyloid), and vitamin E. Many others

under investigation.
5. Monitor and treat mood disorders, behavioral disturbances, etc.

Quick HIT

Patients with AD have decreased acetylcholine synthesis and thus impaired cortical cholinergic function. Cholinesterase inhibitors increase cholinergic transmission by inhibiting cholinesterase.

Altered Mental Status

Acute Encephalopathy

A. Terminology

1. Acute encephalopathy, acute confusional state, and delirium are often used interchangeably.
2. Delirium is included in the DSM-5, with key features of acute onset, loss of attention and awareness, disturbed cognition (memory, language, etc.), caused by a medical condition or medication, and not better explained by another neurocognitive disorder (see Clinical Pearl 5-6) (see Table 5-3).

B. Differential diagnosis (see Figure 5-5)

1. There is a long list of etiologies that can cause acute encephalopathy, and some use the following mnemonics to remember the key categories:
   a. MOVE STUPID
      - Metabolic disorders (e.g., hypercalcemia)
      - Oxygen
      - Vascular (e.g., MI, CVA)
      - Endocrine (e.g., hypoglycemia)
      - Seizure
      - Trauma

- Uremia
- Psychiatric
- Infectious
- Drugs

b. MIST

- Metabolic (e.g., electrolytes, organ injury such as liver or kidney, urinary retention)
- Infection (e.g., CNS, extracranial infections, sepsis)
- Structural (e.g., mass, trauma)
- Toxin (e.g., drugs, withdrawal)

CLINICAL PEARL 5-6

Altered Mental Status

- Consciousness relies on arousal and cognition. Arousal is dependent on an intact brainstem (reticular activating system in brainstem). Cognition is dependent on an intact cerebral cortex.
- Altered mental status, diminished level of consciousness (drowsiness, stupor, coma), and confusion are caused by many of the same conditions and are often variations of the same theme.
- Depressed level of consciousness and coma can be caused by a variety of disorders. To help in classification and to organize one's thinking, it is useful to organize these causes into two categories:
  - Diffuse injury to the brain due to any metabolic, systemic, or toxic disorder
  - Focal intracranial structural lesions—for example, hemorrhage, infarction, tumor

TABLE 5-3 Delirium Versus Dementia		
Feature	**Delirium**	**Dementia**
Causes	• Infections (UTI, systemic infection) • Medications (narcotics, benzodiazepines) • Postoperative delirium (in elderly patients) • Alcoholism • Electrolyte imbalances • Medical conditions (stroke, heart disease, seizures, hepatic and renal disorders)	• Alzheimer disease • Multi-infarct dementia • Pick disease (frontotemporal dementia)
Level of Consciousness	Altered, fluctuating	Preserved
Hallucinations	Frequently present (visual)	Rarely present
Presence of Tremor	Sometimes present (e.g., asterixis)	Usually absent unless dementia is due to Parkinson disease
Course	• Rapid onset, **waxing and waning** • **"Sundowning"** (worsening at night) may be present	Insidious, progressive
Reversibility	Almost always reversible	Typically irreversible

C. Clinical Features

1. In contrast to both dementia and psychosis, delirium is characterized by a rapid deterioration in mental status (over hours to days), a fluctuating level of awareness, disorientation, and attention.
2. Delirium may often be accompanied by acute abnormalities of perception, such as hallucinations.
3. Patients may be agitated (i.e., hyperactive delirium), or have a slow, blunted responsiveness (i.e., hypoactive delirium).
4. The strongest risk factor is preexisting cognitive impairment.

D. Diagnosis

1. The most common delirium screening test is the Confusion Assessment Method (CAM), which is based on four features: acute

onset with a fluctuating course, inattention, disorganized thinking, and an altered level of consciousness.

2. Workup of delirium depends on suspected contributing factors and reversible causes. It is largely based on a good history and physical examination (with a detailed neurologic examination and mental status assessment), especially with a good review of medications. Lab, imaging, and procedures (e.g., LP) workup is patient-specific.

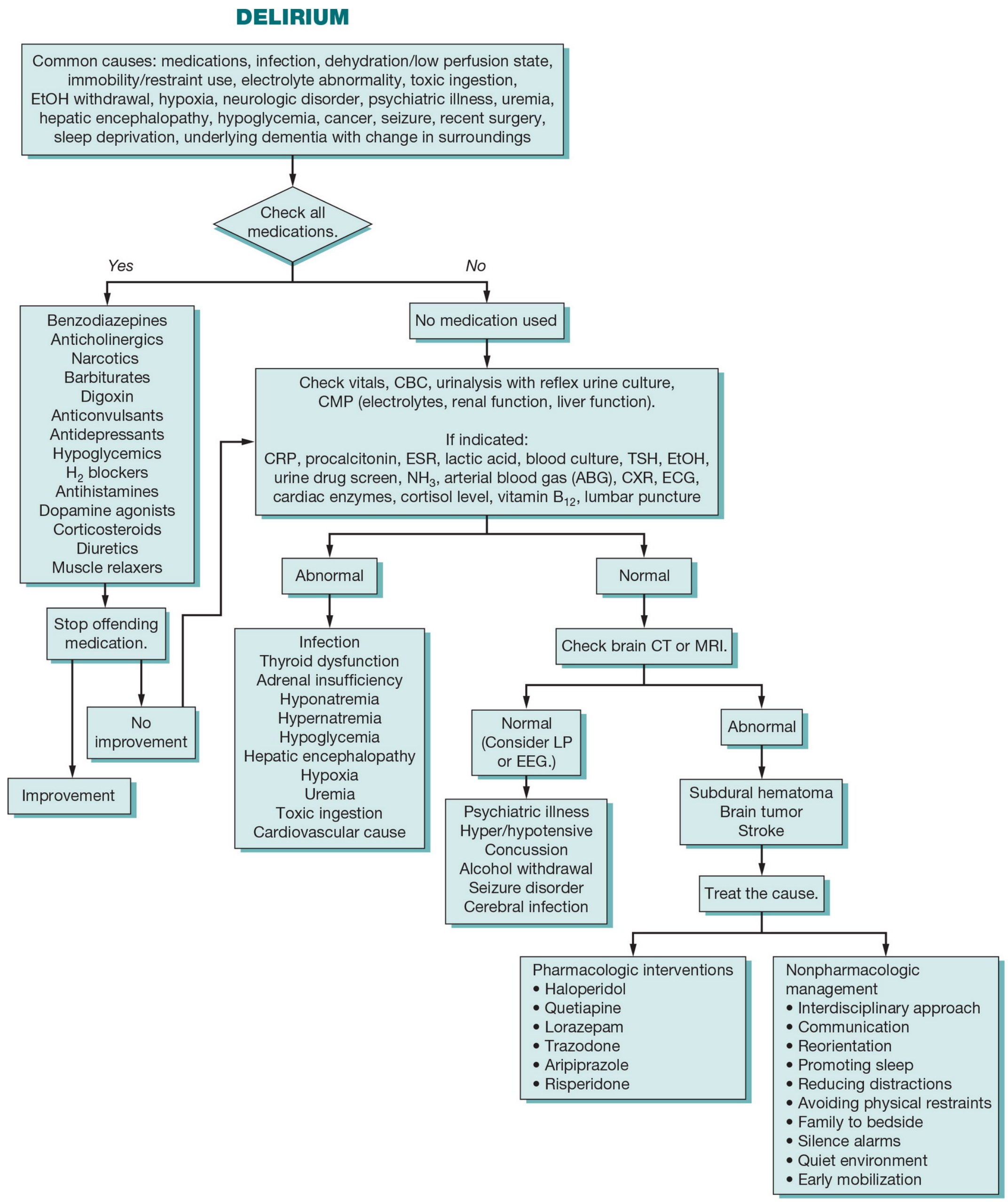


FIGURE 5-5 **Delirium.**
(Reprinted with permission from Domino FJ, Baldor RA, Barry KA, et al. *The 5-Minute Clinical Consult 2023*. 31st ed. Wolters Kluwer; 2022. [Data from Oh ES, Fong TG, Hshieh TT, et al. Delirium in older persons: advances in diagnosis and treatment. *JAMA* 2017;318(12):1161–1174.])

E. Treatment

1. Treat the underlying cause.

2. Delirium precautions while in the hospital: frequent reorientation, familiar objects and faces (i.e., family at the bedside), maintaining a normal sleep–wake cycle with blinds open during the day, and correcting sensory impairments (hearing aids, glasses, etc.).

Avoid restraints and pharmacologic management of agitation as much as possible; if absolutely necessary, antipsychotics such as haloperidol may be used.

A 53-year-old man presents to the hospital accompanied by police officers. He was found walking in the middle of a very busy highway. When asked for his name, age, time, and place, his responses are unintelligible. He has a blood pressure of 154/92 mmHg and a heart rate of 94 beats per minute. Physical examination shows a malnourished patient with dilated pupils that are reactive to light. The patient is noted to have an ataxic broad-based gait.

Which of the following is the best initial treatment for this patient?

A. Haloperidol
B. Naloxone
C. Thiamine
D. Clonidine

- **The answer is C: Thiamine.** This patient is presenting in a disoriented and confused state; the differential is broad and includes infection, intoxication, vitamin deficiency, hypoxia, and several other neurologic conditions. In clinical scenarios in which the patient's history is limited, the provider must immediately attempt to treat reversible causes of confusion. Examples include thiamine (for Wernicke encephalopathy), dextrose (for hypoglycemia), oxygen (for hypoxia), and naloxone (for opiate overdose). Given this patient's ataxia, Wernicke encephalopathy should be suspected. Wernicke encephalopathy typically presents with confusion, ataxia, and ophthalmoplegia and results from a deficiency of thiamine (vitamin B_1). It commonly occurs in alcohol use disorder patients with poor nutrition. Of note, patients should receive thiamine *before* dextrose, since this can actually worsen or even precipitate Wernicke encephalopathy. **(A)** Haloperidol is a typical antipsychotic medication used in the treatment of schizophrenia and psychotic states. This is not used in the treatment of reversible causes of confusion. **(B)** Although naloxone (opioid receptor antagonist) is used for patients with suspected opioid overdose, pinpoint pupils and

respiratory depression would be seen. **(D)** Clonidine is an antihypertensive medication (acts on central alpha-receptors). Although this patient is hypertensive, blood pressures typically need to be higher than 180/120 mmHg to cause hypertensive encephalopathy.

Coma

A. General Characteristics

1. A coma is a depressed level of consciousness to the extent that the patient is completely unresponsive to any stimuli
2. Causes
   a. Structural brain lesions that cause a coma are usually bilateral unless they produce enough mass effect to compress the brainstem or the opposite cerebral hemisphere (see Clinical Pearl 5-7)
   b. Global brain dysfunction (e.g., metabolic or systemic disorders)
   c. Psychiatric causes—conversion disorders and malingering may be difficult to differentiate from a true coma

B. Approach

1. Initial steps
   a. Assess vital signs. ABCs take priority.
   b. Always assume underlying trauma (stabilize cervical spine) and assess the patient for signs of underlying causes of trauma.
   c. Assess the level of consciousness using the Glasgow Coma Scale (see Table 5-4). Repeat this serially because it can change.

CLINICAL PEARL 5-7

Differential Diagnosis of AMS Can Be Remembered by the Mnemonic MOVE STUPID

- Metabolic disorders (e.g., hypercalcemia)
- Oxygen
- Vascular (e.g., MI, CVA)
- Endocrine (e.g., hypoglycemia)
- Seizure
- Trauma
- Uremia
- Psychiatric
- Infectious
- Drugs

2. Approach to diagnosing the cause of coma.
   a. Rapid motor examination—if asymmetry is noted in movements, a mass lesion is the likely cause. Metabolic or systemic causes of coma do not produce asymmetric motor abnormalities.
   b. Brainstem reflexes (see Clinical Pearl 5-8).
      - Pupillary light reflex—If the pupils are round and symmetrically reactive (constrict to bright light), the midbrain is intact and not the cause of coma. Anisocoria (asymmetric pupils) may be a sign of uncal herniation. Keep in mind that certain eye drops or systemic medications may alter pupil size.
      - Eye movements—if the cervical spine is uninjured, perform the oculocephalic test (“doll’s eyes”). When the head is turned to one side, the eyes should move conjugately to the opposite direction if the brainstem is intact.
      - If the patient is breathing on their own, the brainstem is functioning.
   c. Laboratory tests—CBC, electrolytes, calcium BUN, creatinine, glucose, plasma osmolarity, arterial blood gas, ECG.
   d. Toxicologic analysis of blood and urine.
   e. CT or MRI of the brain.
   f. LP—if meningitis or SAH is suspected.

Quick HIT

Assessing the Cause of a Coma

- Abnormal pupillary light reflex—structural intracranial lesions (hemorrhage, mass); drugs that affect the pupil (morphine, atropine-like agents); anoxic encephalopathy; recent eye drops
- Bilateral fixed, dilated pupils—severe anoxia
- Unilateral fixed, dilated pupil—herniation with CN III compression
- Pinpoint pupils—narcotics, ICH

TABLE 5-4 Glasgow Coma Scale

Eye Opening (E)	Does not open eyes	1
	Opens to painful stimulus	2
	Opens to voice (command)	3
	Opens spontaneously	4
Motor Response (M)	No movement	1
	Decerebrate posture	2
	Decorticate posture	3
	Withdraws from pain	4
	Localizes pain stimulus	5
	Obeys commands	6
Verbal Response (V)	No sounds	1
	Incomprehensible sounds	2
	Inappropriate words	3
	Appropriate but confused	4
	Appropriate and oriented	5

CLINICAL PEARL 5-8

Brain Death Versus Persistent Vegetative State

- Criteria for diagnosing brain death:
  - **Irreversible** absence of brain and brainstem function—unresponsiveness, apnea **despite adequate oxygenation and ventilation,** no brainstem reflexes (pupils, calorics, gag, cornea, doll's eyes).
  - No drug intoxication or metabolic condition that can reversibly inhibit brain function.
  - Core body temperature >32°C/89.6°F. Brain death cannot be established in the presence of hypothermia.
  - Clinical evidence or imaging study that provides a causative explanation for brain death.
  - Examinations must be repeated or EEG performed. EEG shows isoelectric activity (electrical silence).
- In most US states, **if a patient is proven to be brain dead,** the physician has the right to disconnect life support—the patient is **legally dead.** (Obviously, sensitivity and consideration must be demonstrated to the family. They must be informed and given a chance to say goodbye to their loved one.)
- Patients in a "vegetative state" are completely unresponsive (comatose), but eyes are open and they appear awake. May have random head or limb movements. Patient **may** have no hope of meaningful recovery but do not meet brain death criteria. Ethical and legal issues surrounding supportive measures are much more complicated.

Quick HIT

"Locked in" Syndrome

- Mimics coma, because patients are completely paralyzed (with sparing of muscles required for respiration, blinking, and vertical eye movement).
- Patients are **fully aware** of their surroundings and capable of feeling pain.
- This is usually caused by infarction or hemorrhage of the ventral pons.

C. Treatment

1. Correct reversible causes and treat the underlying problem (if identified)—control airway; give supplemental oxygen, naloxone (for narcotic overdose), dextrose (for hypoglycemia). Give thiamine before a glucose load. Correct any abnormalities in BP, electrolytes, or body temperature.

2. Identify and treat herniation—lowering the ICP is critical.

Demyelinating Disease

Multiple Sclerosis

A. General Characteristics

1. Pathology
   a. Selective **demyelination of CNS**—multifocal zones of demyelination (plaques) are scattered throughout the white matter. Classic location of plaques is at the angles of the lateral ventricles.
   b. Demyelination primarily involves **white matter** of the brain and spinal cord; tends to spare the gray matter/axons and the peripheral nervous system. However, improved imaging techniques are showing that cortical demyelination may be more prevalent than previously appreciated.
   c. Commonly involved tracts: pyramidal and cerebellar pathways, medial longitudinal fasciculus, optic nerve, posterior columns.
2. Women are two to three times more likely than men to have MS.
3. Etiology is unknown, but is probably secondary to the interplay of environmental, immunologic, and genetic factors.

Quick HIT

MS is a clinical diagnosis based on multiple CNS lesions separated by time and space. This may be clinical findings alone, or more commonly a combination of clinical findings with radiologic findings.

B. Clinical Features

1. Transient sensory deficits
   a. Most common initial presentation
   b. Decreased sensation or paresthesias in upper or lower limbs.
2. Fatigue—one of the most common complaints

3. Motor symptoms—mainly weakness or spasticity
   a. May appear insidiously or acutely.
   b. Caused by pyramidal tract involvement (upper motor neuron involvement).
   c. Spasticity (such as leg stiffness) can impair the patient's ability to walk and maintain balance.
   d. Can lead to weakness with progression to paraparesis, hemiparesis, or quadriparesis.

Quick HIT

Relapses of MS produce symptoms for longer than 24 hours. They average one per year, but usually decrease in frequency over time.

4. Visual disturbances
   a. **Optic neuritis**
      - Monocular visual loss (in up to 20% of patients), often with pain during eye movement.
      - May have central scotoma (black spot in center of vision) or decreased pupillary reaction to light.
   b. **Internuclear ophthalmoplegia**—strongly suggests the diagnosis. A lesion in the medial longitudinal fasciculus results in ipsilateral medial rectus palsy on attempted lateral gaze (adduction defect) and horizontal nystagmus of abducting eye (contralateral to side of lesion). Diplopia can occur.
5. Cerebellar involvement—can cause ataxia, intention tremor, dysarthria.
6. Loss of bladder control—consequence of upper motor neuron injury in spinal cord.
7. Autonomic involvement—may present as impotence and/or constipation.
8. Cerebral involvement—may occur in advanced illness and manifests as memory loss, personality change, and emotional lability; anxiety and depression are common.
9. Neuropathic pain—a frustrating but common complaint that manifests as hyperesthesia and trigeminal neuralgia.

C. Course

1. Most patients at initial presentation are in their 20s to 30s and present with a localizing deficit such as optic neuritis, one-sided weakness, or numbness. Patients may or may not go on to develop MS. The initial presentation is termed a clinically isolated syndrome, since it is not sufficient to fulfill MS diagnostic criteria.
2. Relapsing-remitting MS is the pattern of flares (relapses) followed by either full recovery or partial recovery with residual deficits, creating a new baseline.
3. Secondary progressive MS often starts with a relapse-remitting pattern, then changes to a gradual worsening of disease that may or may not involve obvious flares.
4. Primary progressive MS has a progressive course of accumulating disability from the onset, and represents about 10% of patients.

D. Diagnosis

1. The diagnosis is essentially clinical—suspect it in young adults with relapsing and remitting neurologic signs and symptoms that are difficult to explain (due to involvement of different areas of CNS white matter). Nevertheless, on suspicion, order the MRI and consider LP (discussed below), because it is important to diagnose MS with as much certainty as possible due to the implications surrounding the management approach.
   a. The 2017 McDonald Criteria for the diagnosis of MS requires ruling out more likely neurologic diseases and demonstrating CNS lesions separated in time and space. The diagnosis can be confirmed with only one clinical attack, as long as there is supporting radiologic (MRI) or laboratory (CSF-specific oligoclonal bands) evidence.
2. MRI is the most sensitive test and is diagnostic in the majority of cases.
   a. The number of lesions on the MRI is **not** necessarily proportional to disease severity or speed of progression.
3. LP and CSF analysis—Although no laboratory tests are specific for MS, **oligoclonal bands** of immunoglobulin G are present in 90% of MS patients.

4. Evoked potentials can suggest demyelination of certain areas by measuring the speed of nerve conduction within the brain: newly remyelinated nerves will conduct sensory impulses more slowly.

Quick HIT

Diagnostic Tests for MS (helpful hints)

- MRI is abnormal in 90% of MS patients.
- CSF is abnormal in 90% of MS patients.
- Evoked potentials are abnormal in 90% of MS patients.

Quick HIT

There is no cure for MS. There are two primary goals:

- Prevent relapses
- Relieve symptoms of acute exacerbations

E. Treatment

1. Treatment of acute attacks
   a. High-dose IV corticosteroids can shorten an acute attack.
   b. Plasma exchange may be used for patients with a poor response to steroids.
   c. Studies have shown that treatment of acute exacerbations does not alter the outcome or course of MS.
   d. Most acute attacks resolve within 6 weeks with or without treatment.
2. Disease-modifying therapy
   a. There are many newer therapies, and management options are evolving. Therapy should be started early to avoid progressive, irreversible disability.
   b. The most common initial treatments include natalizumab, ocrelizumab, alemtuzumab, ofatumumab, and cladribine. The older injection therapies are less effective and include interferon-based therapies (e.g., interferon β-1a) and glatiramer.
   c. Natalizumab is a very effective infusion therapy, especially for those with active disease, though it increased the risk of progressive

multifocal leukoencephalopathy.

d. Often the choice of agent involves patient-specific factors and preferences.

3. Symptomatic therapy:
   a. Baclofen or dantrolene for muscle spasticity
   b. Carbamazepine or gabapentin for neuropathic pain
   c. Treat depression if indicated

Quick HIT

IV steroids help hasten recovery of the acute episode in MS but do not result in any improvement in long-term outcome.

Guillain–Barré Syndrome

A. General Characteristics

1. Inflammatory demyelinating polyneuropathy that primarily affects motor nerves, but has many variants (e.g., Miller Fisher syndrome). The most common form of Guillain–Barré syndrome is acute inflammatory demyelinating polyneuropathy.
2. Usually preceded by a viral or mycoplasma infection of the upper respiratory or GI tract. Other common infections include *Campylobacter jejuni,* CMV, hepatitis, and HIV.
3. May also occur in Hodgkin disease, lupus, after surgery, or after HIV seroconversion.

Quick HIT

Prognosis for Guillain–Barré Syndrome

- Signs of recovery within 1 to 3 weeks after onset favor a good prognosis. If illness continues for a longer period (e.g., beyond 6 weeks), a chronic relapsing course is more likely and prognosis is less favorable.
- It may take months before the patient recovers. A minority of patients experience recurrent attacks, and about 5% die due to respiratory failure, pneumonia, or arrhythmias.

B. Clinical Features

1. Abrupt onset with rapidly **ascending weakness/paralysis** of all four extremities; frequently progresses to involve respiratory, facial, and bulbar muscles.
   a. Usually symmetric (but not always).
   b. Weakness may be mild or severe.
   c. Weakness usually progresses from distal to central muscles.
   d. **If generalized paralysis is present, it can lead to respiratory arrest.**
2. Extremities may be painful, but sensory loss is not typical.
3. Sphincter control and mentation are typically spared.
4. Autonomic features (e.g., arrhythmias, tachycardia, postural hypotension) are dangerous complications.

Quick HIT

Diagnosis made by a combination of CSF fluid analysis, clinical findings, and nerve conduction velocities.

C. Diagnosis

1. CSF analysis—elevated protein, but normal cell count.
2. Electrodiagnostic studies—decreased motor nerve conduction velocity.

D. Treatment

1. Carefully monitor pulmonary function. Mechanical ventilation may be necessary.
2. Administer IV immunoglobulin or plasma exchange.
3. Do **not** give steroids. They are not helpful in Guillain–Barré syndrome.

Quick HIT

In Guillain–Barré syndrome, rapid progression to respiratory failure can occur within hours. Therefore, a timely and accurate diagnosis is critical. If you suspect Guillain–Barré syndrome, immediately admit the patient to the hospital for monitoring.

Neuromuscular Diseases

Myasthenia Gravis

A. General Characteristics

1. **Autoimmune disorder**—Autoantibodies are directed against the nicotinic acetylcholine receptors of the neuromuscular junction, which leads to a reduced postsynaptic response to acetylcholine and results in significant muscle fatigue.
2. Muscles that are stimulated repeatedly (e.g., extraocular muscles) are prone to fatigue.
3. The peak incidence in women is ages 20 to 30; in men, 50 to 70. It is more common in women.

CLINICAL PEARL 5-9

Lambert–Eaton Myasthenic Syndrome

- Associated with small cell lung cancer
- Caused by autoantibodies directed against **presynaptic** calcium channels
- Clinical features include proximal muscle weakness and hyporeflexia
- Distinguished from myasthenia gravis in that symptoms **improve** with repeated muscle stimulation

B. Clinical Features

1. **Skeletal muscle weakness**—with preservation of sensation and reflexes.
   a. Weakness is exacerbated by continued use of muscle and improved by rest (see Clinical Pearl 5-9). Symptoms worsen toward the end of the day (due to fatigue).
   b. Involved muscles vary and may include the following:
      - Cranial muscles: extraocular muscles, eyelids (ptosis), facial muscles (facial weakness, difficulty in chewing, slurred speech).
      - Limb muscles (proximal and asymmetric).

2. Ptosis, diplopia, and blurred vision—most common initial symptoms.
3. Generalized weakness, dysarthria, and dysphagia.
4. The condition progresses slowly with periodic exacerbations. **Myasthenic crisis is a medical emergency that occurs in 15% of patients.** Diaphragm and intercostal fatigue result in respiratory failure, often requiring mechanical ventilation.

Quick HIT

Myasthenia gravis may be limited to extraocular muscles, especially in elderly patients.

C. Diagnosis

1. Acetylcholine receptor antibody test is the test of choice (most specific). Nevertheless, 20% of patients with clinical manifestations of myasthenia gravis may be "antibody negative."
2. EMG shows a decremental response to repetitive stimulation of motor nerves.
3. A CT scan of the thorax can rule out **thymoma.** Thymoma is present in only 10% to 15% of patients, but the thymus is histologically abnormal in 75% of patients.
4. Edrophonium (Tensilon) test—anticholinesterase (AChE) medications cause marked improvement of symptoms, but a high false-positive rate limits utility.

D. Treatment

1. AChE inhibitors—for example, pyridostigmine
   a. Inhibiting AChE increases concentration of acetylcholine at the synapse by decreasing the breakdown of acetylcholine.
   b. This is a symptomatic benefit only.
2. Thymectomy
   a. This provides a symptomatic benefit and complete remission in many patients, even in the absence of a thymoma.
   b. Although usually benign, thymoma is an absolute indication for thymectomy.
3. Immunosuppressive drugs

a. Use corticosteroids for patients with a poor response to AChE inhibitors.
b. Azathioprine and cyclosporine are alternative third-line agents.

4. Plasma exchange removes antibodies to acetylcholine receptors. Use it if all else fails or if the patient is in respiratory failure.
5. IV immunoglobulin therapy is now sometimes used for acute exacerbations.
6. Monitor serial forced vital capacities. A forced vital capacity of 15 mL/kg (about 1 L) is generally an indication for intubation. **Patients in myasthenic crisis have a low threshold for intubation—do not wait until the patient is hypoxic.**

***Quick* HIT**

Medications that exacerbate symptoms of myasthenia gravis

- Antibiotics—aminoglycosides, fluoroquinolones, and others
- β-Blockers
- Antiarrhythmics—quinidine, procainamide, and lidocaine
- Many others

A 27-year-old woman presents with fatigue and double vision. The patient reports that these symptoms occur at the end of a “long work day.” The patient also reports that she does not eat “tough” foods anymore such as steak or chicken as it is difficult for her to chew. Neurologic examination is unremarkable and the patient has normal thyroid-stimulating hormone (TSH) and creatine kinase (CK) levels. The diagnosis is confirmed with a special laboratory test.

Which of the following is the next best step in management of this patient?

A. MRI of the head
B. CT scan of the chest
C. CT scan of the abdomen
D. Ultrasound of the neck

- **The answer is B: CT scan of the chest.** The patient in this question is suffering from myasthenia gravis (MG), an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatigue. The main symptom of MG is muscle weakness *after* a period of muscle use. Extraocular muscles are commonly involved leading to double vision. Jaw fatigue is common as well due to fatigue of the bulbar muscles. The underlying mechanism of MG is circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction. In contrast, Lambert–Eaton syndrome has autoantibodies directed at presynaptic voltage-gated calcium channels. Of note, about 15% of patients with MG will have a thymoma, so it is critical to perform a CT scan of the chest after the diagnosis is made. **(A, C, D)** These are not the most appropriate first steps in management after the diagnosis of MG is made. A thymoma must first be excluded.

Duchenne Muscular Dystrophy

A. General Characteristics

1. **X-linked recessive** (almost exclusively in **males**) disease involving a mutation on a gene that codes for the dystrophin protein (dystrophin is absent causing muscle cells to die).
2. Characteristically, there is **no inflammation.**

B. Clinical Features

1. Muscle weakness is progressive, symmetric, and starts in childhood. Proximal muscles primarily affected (pelvic girdle). Eventually involves the respiratory muscles.
2. *Gowers maneuver*—patient uses hands to get up from floor because the weakness in the proximal lower extremity muscles makes it difficult to arise without support.
3. Enlarged calf muscles—true muscle hypertrophy at first, followed by **pseudohypertrophy** as fat replaces muscle.
4. Ultimately results in wheelchair confinement, respiratory failure, and death in third decade.

C. Diagnosis

1. Serum creatine phosphokinase—levels are markedly elevated.
2. DNA testing has now replaced muscle biopsy for diagnosis.

D. Treatment

1. Prednisone is beneficial and is associated with a significant increase in strength, muscle function, and pulmonary function and may reduce risk of scoliosis. Chronic steroid treatment does have side effects, but it is recommended for boys 5 years of age and older whose motor skills are declining.
2. Surgery to correct progressive scoliosis is often necessary once patient becomes wheelchair dependent.

Becker Muscular Dystrophy

- Less common than Duchenne muscular dystrophy

- Also X-linked recessive
- Similar to Duchenne muscular dystrophy, but there is **later onset and a less severe course.** Some dystrophin is present

> ***Quick* HIT**
>
> **Other Hereditary Causes of Muscle Weakness**
>
> - Mitochondrial disorders: associated with maternal inheritance and ragged red muscle fibers
> - Glycogen storage diseases such as McArdle disease (autosomal recessive, muscle cramping after exercise due to glycogen phosphorylase deficiency)

Neurocutaneous Syndromes

Neurofibromatosis Type I (von Recklinghausen Disease)

- **Autosomal dominant** disease characterized by café-au-lait spots, neurofibromas, CNS tumors (gliomas, meningiomas), axillary or inguinal freckling, iris hamartomas (*Lisch nodules*), bony lesions.
- Cutaneous neurofibromas—may be disfiguring.
- Complications include scoliosis, pheochromocytomas, optic nerve gliomas, renal artery stenosis, and erosive bone defects. Musculoskeletal manifestations include spinal deformity and congenital tibial dysplasia.
- Complications may require treatment. Surgically excise any symptomatic neurofibromas.

> ***Quick* HIT**
>
> Other features that may be present in neurofibromatosis patients (both types)
>
> - Seizures
> - Mental retardation, learning disabilities
> - Short height
> - Macrocephalic

Neurofibromatosis Type II

- **Autosomal dominant** disease; less common than type I neurofibromatosis.
- Clinical features include bilateral (sometimes unilateral) acoustic neuromas (classic finding), multiple meningiomas, café-au-lait spots, neurofibromas (much less common than type I), and cataracts.

> ***Quick* HIT**
>
> In patients with neurofibromatosis, prognosis depends on the type and number of tumors and their location. Most patients can function well.

Tuberous Sclerosis

- Usually autosomal dominant.
- Presents with cognitive impairment, epilepsy, and skin lesions (including facial angiofibromas, adenoma sebaceum).
- Retinal hamartomas, renal angiomyolipomas, and rhabdomyomas of the heart may also be present.
- Treat complications.

Sturge–Weber Syndrome

- Acquired disease.
- Key pathologic feature is the presence of capillary angiomatoses of the pia mater.
- Classic feature is facial vascular nevi (port-wine stain).
- Epilepsy and mental retardation are usually present.
- Treatment of epilepsy is often the mainstay of treatment.

Von Hippel–Lindau Disease

- Autosomal dominant.
- Important features are cavernous hemangiomas of the brain or brainstem, renal angiomas, and cysts in multiple organs.
- Associated with renal cell carcinoma.

- Associated with pheochromocytomas.

Spinal Cord Diseases

Syringomyelia

- Central cavitation of the cervical cord due to abnormal collection of fluid within the spinal cord parenchyma (Figure 5-6).
- Most commonly associated with Arnold–Chiari malformation. Other causes are posttraumatic, postinfectious, tethered cord, intramedullary tumors.
- Clinical features—most often asymptomatic and discovered incidentally on MRI obtained for other reasons. Symptoms may include **bilateral loss of pain** and temperature sensation over the shoulders in a **"cape-like" distribution** (lateral spinothalamic tract involvement), preservation of touch, thoracic scoliosis, and muscle atrophy of the hands may occur.
- Diagnosed by MRI.
- Treatment depends on size of syrinx, symptoms, and associated findings (Chiari, tethered cord). Evaluation by neurosurgery recommended.

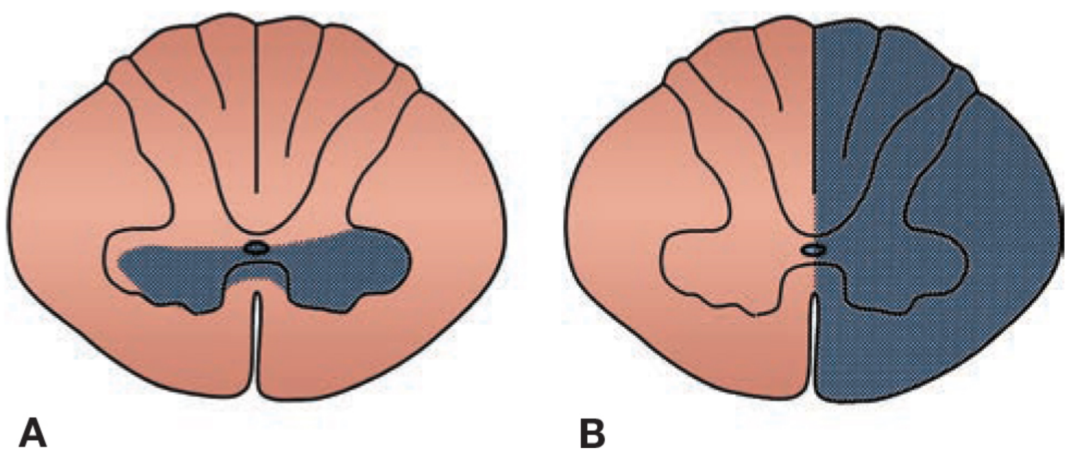


FIGURE 5-6 **Classic lesions of the spinal cord. A: Syringomyelia. B: Hemisection of the spinal cord (Brown-Séquard syndrome).** (Reprinted with permission from Fix JD. *High-Yield Neuroanatomy*. 2nd ed. Lippincott Williams & Wilkins; 2000:46. Figures 8-2H and E, respectively.)

Brown-Séquard Syndrome

- Spinal cord hemisection (i.e., lesion involving either the right or the left half of the spinal cord), usually at the cervical levels (where spinal cord enlarges) (see Figure 5-6).
- Causes include trauma (e.g., fracture, stab wound) that causes hemisection of spinal cord or most commonly, a crush injury to one side of spinal cord, tumors, and abscesses (less common).
- Clinical features: **contralateral loss of pain and temperature** (spinothalamic tract), **ipsilateral hemiparesis** (corticospinal tract), and **ipsilateral loss** of position/vibration (dorsal columns).
- Prognosis for neurologic recovery is very good.

Transverse Myelitis

- This is a rare condition that specifically affects the tracts across the horizontal aspect of the spinal cord at a given level. The thoracic spine is the most commonly involved.
- The cause is usually unknown, but it can occur after viral infections. Progression is usually rapid.
- Clinical features include lower extremity weakness or plegia, back pain, sensory deficits below the level of the lesion, and sphincter disturbance (especially urinary retention).
- MRI with contrast is the imaging study of choice.
- High-dose steroid therapy is often used, but evidence supporting its use is equivocal.
- The prognosis is highly variable and unpredictable, ranging from full recovery to death.

Horner Syndrome

A. General Characteristics

1. Results from the interruption of cervical sympathetic nerves.
2. Can be preganglionic (central lesions) or postganglionic (distal to superior cervical ganglion); the former is more worrisome and requires more thorough evaluation.

B. Clinical Features

1. Ipsilateral **ptosis**—mild drooping of lid (levator palpebrae still intact)
2. Ipsilateral **miosis**—“pinpoint pupil”
3. Ipsilateral **anhidrosis** (decreased sweating on forehead)—may be difficult to detect

C. Causes

1. Idiopathic (most cases)
2. Pancoast tumor (pulmonary neoplasm of the superior sulcus at lung apex)
3. Internal carotid dissection
4. Brainstem stroke
5. Neck trauma (cervical spine injury)

Poliomyelitis

- Poliovirus affects the anterior horn cells and motor neurons of spinal cord and brainstem. Causes lower motor neuron involvement.
- Characteristic features include asymmetric muscle weakness (legs more commonly involved); absent deep tendon reflexes; flaccid, atrophic muscles; and **normal sensation.**
- Bulbar involvement (of CN IX and CN X) in 10% to 15% of cases can lead to respiratory and cardiovascular impairment.
- No treatment is available, although poliomyelitis is entirely preventable by vaccination.

Miscellaneous Conditions

Vertigo

A. General Characteristics (Clinical Pearl 5-10)

1. Vertigo refers to a disturbance of the vestibular system characterized by a sensation of spinning or hallucination of movement.

2. It is important to identify the common complaint of “dizziness” as vertigo (“room spinning”) or lightheadedness (presyncopal symptoms from cerebral hypoperfusion).
3. The initial goal is to determine whether the cause of the vertigo is peripheral (inner ear) or central (e.g., tumor, CVA).
4. Peripheral vertigo is usually benign, but central vertigo can have serious consequences.
5. For patient with ongoing symptoms (continuous vertigo), perform a HINTS test to rule out brainstem or cerebellar stroke. HINTS is a three-part test and stands for Head Impulse, Nystagmus, and Test for Skew. The presence of all three of the following suggests a peripheral lesion, and is accurate in ruling out a central lesion: abnormal head impulse test, the presence of unidirectional, horizontal, or torsional nystagmus, and absent skew.

Quick HIT

In a patient with vertigo, goal is to differentiate between peripheral (benign) and central (worrisome) vertigo (see Table 5-5). The HINTS examination may help differentiate central from peripheral vertigo and may be more sensitive than MRI for acute stroke!

B. Types of Peripheral Vertigo

1. Benign positional vertigo (BPV)
   a. Vertigo is experienced only in specific positions or during change in position and lasts for a few moments. It has an abrupt onset as soon as the particular position is assumed.
   b. Usually presents in patients over 60 years old. Treat with meclizine.
   c. Recovery is usually complete (resolves within 6 months).
2. Ménière disease
   a. Triad of **vertigo, tinnitus, and hearing loss.**
   b. Attacks may last for hours to days and recur several months or years later.
   c. The hearing loss eventually becomes permanent.
   d. Treat with sodium restriction and diuretics.

3. Acute labyrinthitis—due to viral infection of the cochlea and labyrinth; may last for several days
4. Ototoxic drugs (aminoglycosides, some loop diuretics)
5. Acoustic neuroma (schwannoma) of the 8th cranial nerve—ataxia, gait unsteadiness, nystagmus, hearing loss, tinnitus

Quick HIT

Hearing loss and tinnitus only occur with peripheral vertigo. Focal neurologic problems only occur with central vertigo.

Quick HIT

Meclizine is useful for vertigo and as an antiemetic. It has anticholinergic and antihistamine effects.

CLINICAL PEARL 5-10

Vertigo

Central Vertigo

- Gradual onset; other neurologic (brainstem) findings are present in most cases (e.g., weakness, hemiplegia, diplopia, dysphagia, dysarthria, facial numbness). Look for cardiovascular risk factors.
- Accompanying nystagmus can be bidirectional or vertical (does not occur in peripheral vertigo).

Peripheral Vertigo

- Lesions are cochlear or retrocochlear.
- Abrupt onset, nausea/vomiting, head position has strong effect on symptoms. Other brainstem deficits are absent, except for tinnitus/hearing loss.

TABLE 5-5 Central Versus Peripheral Vertigo

Central Vertigo	Peripheral Vertigo
Gradual onset	Sudden onset
Mild intensity	Severe intensity
Mild nausea/vomiting	Intense nausea/vomiting
Associated neurologic findings typically present	No associated neurologic findings
Mild nystagmus	Relatively intense nystagmus
Position change has mild effect	Position change has intense effect
No refractoriness—can repeat the "tilt" test and patient responds every time	Rapidly refractory—cannot repeat the "tilt" test; patient will not respond again
Patient falls to same side as lesion	Patient falls to same side as lesion
Direction of nystagmus: multidirectional and even vertical	Direction of nystagmus: unilateral vertical; nystagmus is never peripheral

C. Causes of Central Vertigo

1. MS—demyelination of vestibular pathways of brainstem
2. Vertebrobasilar insufficiency
3. Migraine-associated vertigo—headache may or may not be present

Amyotrophic Lateral Sclerosis or "Lou Gehrig Disease"

A. General Characteristics

1. A disorder affecting the anterior horn cells and corticospinal tracts at many levels. Corticobulbar involvement is common as well. **The presence of upper and lower motor neuron signs is a hallmark of amyotrophic lateral sclerosis (ALS).** Note that only the motor system is involved.
2. Onset is usually between 50 and 70 years of age. (Lou Gehrig was unusually young [in his 30s] when the disease developed.) Occurrence of ALS before age 40 is uncommon.

3. Only 10% of cases are familial, with the remainder being sporadic.
4. Prognosis is dismal: 80% mortality rate at 5 years; 100% mortality rate at 10 years.

Quick HIT

Initially ALS can involve virtually any muscle, but as the disease progresses, every region of the body becomes symmetrically involved.

B. Clinical Features

1. **Progressive muscle weakness is the hallmark feature**
   a. Usually first noted in the legs or arms, but then spreads to other muscle groups
   b. No associated pain
   c. Muscle atrophy
2. Muscle cramps and spasticity
3. Fasciculations (unnoticed by patient)
4. Impaired speech and swallowing; dysphagia can lead to aspiration
5. Respiratory muscle weakness—dyspnea on exertion, and later, at rest; orthopnea; sleep apnea; end-stage ALS is characterized by respiratory failure
6. Weight loss and fatigue
7. The following are normal and unaffected, even in late stages:
   a. Bowel and bladder control
   b. Sensation
   c. Cognitive function
   d. Extraocular muscles
   e. Sexual function

C. Diagnosis

1. There is no specific diagnostic test for ALS. EMG and nerve conduction studies can confirm degeneration of lower motor neurons and can rule out neuromuscular junction disorders
2. Clinical or electrical evidence
   a. Involvement of two regions (probable ALS)

b. Involvement of three to four regions (definite ALS)—affected regions include bulbar (face, larynx, tongue, jaw), cervical, thoracic, and lumbosacral

D. Treatment

1. Treatment has been very disappointing and is mainly supportive.
2. Riluzole is a glutamate-blocking agent—it is the only agent that modestly slows the progression of ALS and delays death by 3 to 5 months.

Quick HIT

EMG and Nerve Conduction Studies

- EMG measures the contractile properties of skeletal muscles
- Lower motor neuron lesions: fibrillations and fasciculations at rest
- Myopathy: No electrical activity at rest (as expected), but amplitude decreases with muscle contraction
- Nerve conduction studies
- Demyelination decreases nerve conduction velocity (MS, Guillain–Barré syndrome)
- Repetitive stimulation causes fatigue (myasthenia gravis)

Aphasia

A. General Characteristics

1. Aphasia is the **loss or defect of language** (e.g., in speaking, fluency, reading, writing, comprehension of written or spoken material).
2. Most lesions that cause aphasia involve the **dominant hemisphere.**
   a. In 95% of right-handed people, the left cerebral hemisphere is dominant for language.
   b. In 50% of left-handed people, the left hemisphere is dominant for language (however, the right hemisphere also has language functions in most left-handed people).
3. There are four types of aphasia (described below): Wernicke aphasia, Broca aphasia, conduction aphasia, and global aphasia.

B. Causes

1. Stroke (most common cause)
2. Trauma to brain
3. Brain tumor
4. Alzheimer disease

Quick HIT

The most common cause of aphasia is cerebrovascular disease. In aphasia, when speech is fluent, the lesion is posterior to the central sulcus. When speech is nonfluent, the lesion is anterior to the central sulcus.

C. Types of Aphasia

1. Wernicke aphasia
   a. Receptive, fluent aphasia
   b. **Impaired comprehension of written or spoken language (key feature)**
   c. **Speech is grammatically correct and is fluid but does not make much sense.** Patients articulate well but often use the wrong words because they cannot understand their own words
2. Broca aphasia
   a. Expressive, nonfluent aphasia
   b. Speech is slow and requires effort
   c. The patient uses short sentences (as few words as possible) without grammatical construction. The content is appropriate and meaningful
   d. Good comprehension of language (written and spoken)
   e. Often associated with a right hemiparesis and hemisensory loss
3. Conduction aphasia
   a. Disturbance in repetition
   b. Pathology involves the connections between Wernicke and Broca areas
4. Global aphasia
   a. Disturbance in all areas of language function (e.g., comprehension, speaking, reading, fluency)
   b. Often associated with a right hemiparesis

D. Treatment of Aphasia

1. Most patients spontaneously recover or improve within the first month.
2. Speech therapy is helpful, but is unlikely to be of much benefit after the first few months.

Bell Palsy

A. General Characteristics

1. This refers to hemifacial weakness/paralysis of muscles innervated by **CN VII** due to swelling of the cranial nerve.
2. The prognosis is very good; 80% of patients recover fully within weeks to months.

B. Causes

1. Cause is often uncertain.
2. Possible viral etiology (herpes simplex)—immunologic and ischemic factors implicated as well.
3. Upper respiratory infection is a common preceding event.

C. Clinical Features

There is acute onset of unilateral facial weakness/paralysis. Both upper and lower parts of the face are affected.

D. Diagnosis

1. Diagnosis is clinical, but consider Lyme disease in endemic areas as the treatment approach is different.
2. **Do not use steroids if Lyme is suspected!**
3. Consider EMG testing if paresis fails to resolve within 10 days.

Quick HIT

Differential Diagnosis for Facial Nerve Palsy

- Trauma (e.g., temporal bone, forceps delivery)
- Lyme disease
- Tumor (acoustic neuroma, cholesteatoma, neurofibroma)
- Guillain–Barré syndrome (palsy is usually bilateral)
- Herpes zoster

E. Treatment

1. Usually none is required, as most cases resolve in 1 month.
2. Short course of steroid therapy (prednisone) and acyclovir, if necessary.
3. Patient should wear eye patch at night to prevent corneal abrasion (cornea is exposed due to weakness of orbicularis oculi muscle).
4. Surgical decompression of CN VII is indicated if the paralysis progresses or if tests indicate deterioration.

Trigeminal Neuralgia (Tic Douloureux)

A. General Characteristics

1. Trigeminal neuralgia is one of the most painful conditions known to mankind.
2. Usually idiopathic in origin.

Quick HIT

Trigeminal Neuralgia

- Complete, spontaneous resolution in 85% of cases
- Mild residual disease in 10% of cases
- No resolution in 5% of cases

B. Clinical Features

1. Brief (seconds to minutes) but frequent attacks of severe, lancinating facial pain

2. Involves the jaw, lips, gums, and maxillary area (ophthalmic division is less commonly affected)
3. Recurrent attacks may continue for weeks at a time
4. No motor or sensory paralysis

C. Diagnosis

1. Clinical diagnosis
2. MRI—to rule out cerebellopontine angle tumor

D. Treatment

1. Drug of choice is **carbamazepine** (usually effective in relieving pain); other choices are baclofen and phenytoin, either alone or in combination with carbamazepine.
2. Consider surgical decompression if medical therapy fails.
3. Patients typically experience a remitting/relapsing course. Over time, pain may become more refractory to treatment.

How to Localize a Neurologic Lesion

A. Introduction

1. In general, neurologic deficits can be localized to one of the following 10 sites:
   a. Cerebral cortex
   b. Subcortical area
   c. Cerebellum
   d. Brainstem
   e. Spinal cord
   f. Plexus (plexopathy)
   g. Roots (radiculopathy)
   h. Peripheral nerve (peripheral neuropathy)
   i. Neuromuscular junction
   j. Muscle (myopathy)
2. Lesions in each of the above sites present with different neurologic findings. A good understanding of the deficits that accompany each lesion can help with localization

B. Cerebral Cortex

1. Lesions in the cerebral cortex often cause two main deficits:
   a. **Contralateral** motor or sensory deficits (depending on which region of the cortex is involved)
   b. Aphasia
2. The hemiparesis seen with cortical lesions primarily affects the face, arms, and trunk. The legs may be affected, but typically that deficit is not as severe. This is because the neurons that control the lower extremities are in the interhemispheric fissure (see homunculus in Figure 5-7)
3. Aphasia is common when the left hemisphere is involved. Visual-spatial deficits are more common when the right hemisphere is involved

C. Subcortical Lesions

1. These involve the internal capsule, cerebral peduncles, thalamus, and pons.
2. The hemiparesis is usually complete (face, arm, leg) because the neurons controlling these structures all merge together subcortically and are very close together.

D. Cerebellum

Incoordination, intention tremor, ataxia

E. Brainstem

1. Cranial nerve and spinal cord findings
2. There is a **crossed** hemiplegia (deficit on ipsilateral face and contralateral body) because the corticospinal tract, dorsal columns, and spinothalamic tracts cross but the cranial nerves do not

F. Spinal Cord

1. With acute injuries, spinal shock may be present and upper motor neuron signs may not be apparent initially.
2. The patient presents with upper motor neuron signs (spasticity, increased deep tendon reflexes, clonus, positive Babinski sign), but

these signs may be present with lesions in the brainstem and cortical/subcortical regions as well.

3. There is a decrease in sensation below a sharp band in the abdomen/trunk. A pinprick is felt above this level but not below it. This is pathognomonic for spinal cord disease—the level of the lesion corresponds to the sensory level.

G. Plexus (Plexopathy)

1. Deficits (motor and sensory) involve **more than one nerve.** Findings are variable depending on which part of the plexus is involved.
2. Trauma is the most common cause overall, especially for the brachial plexus. A postsurgical hematoma in the pelvis is a more common cause in lumbosacral plexopathy.
3. Plexuses that are commonly involved include:
   a. Brachial plexus—Erb–Duchenne type is the more common (upper trunk—C5-6 roots). Lower trunk (C8-T1) is less common
   b. Lumbosacral plexus (L5–S3)

H. Roots (Radiculopathy)

1. Pain is a key finding.
2. This affects a group of muscles supplied by a spinal root (myotome) and a sensory area supplied by a spinal root (dermatome). Therefore, the distribution of affected areas can help differentiate this from a peripheral neuropathy or a plexopathy.
3. Patients may present with weakness, atrophy, and sensory deficits in a dermatomal pattern; may include fasciculations and diminished deep tendon reflexes.

I. Peripheral Nerve (Peripheral Neuropathy)

1. Weakness is more prominent distally at the outset (as opposed to muscle myopathy [see below])—**usually asymmetric.**
2. Presents with diminished deep tendon reflexes; may include sensory changes (numbness, paresthesias, tingling), muscle atrophy, and fasciculations.
3. Can be due to **diabetes** (nerve infarction), trauma, entrapment, or vasculitis.

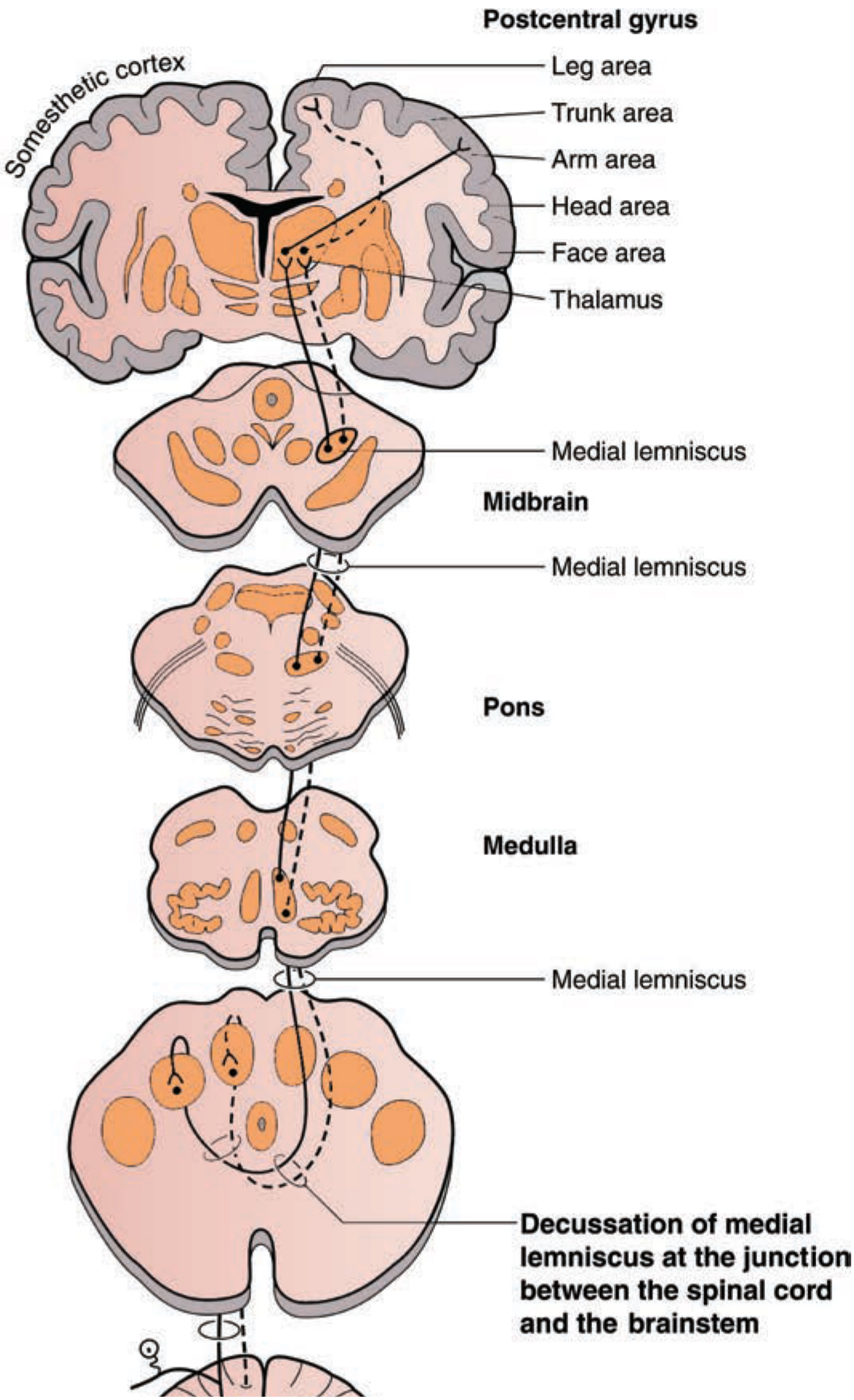
4. Common neuropathies include radial/ulnar/median/musculocutaneous nerves, long thoracic nerve, axillary nerve, common peroneal nerve, and femoral nerve.

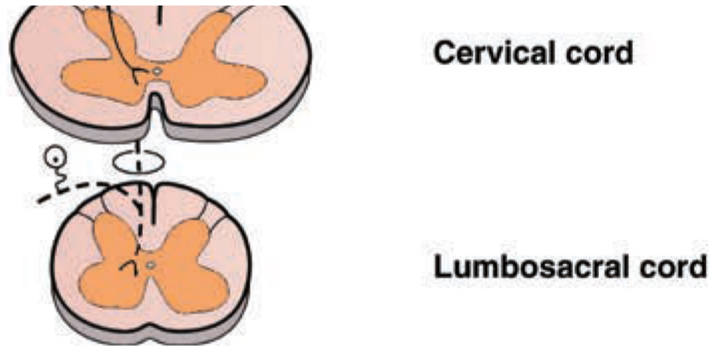
J. Neuromuscular Junction

1. Fatigability is the key finding. Muscles become weaker with use and recover with rest
2. Normal sensation, no atrophy

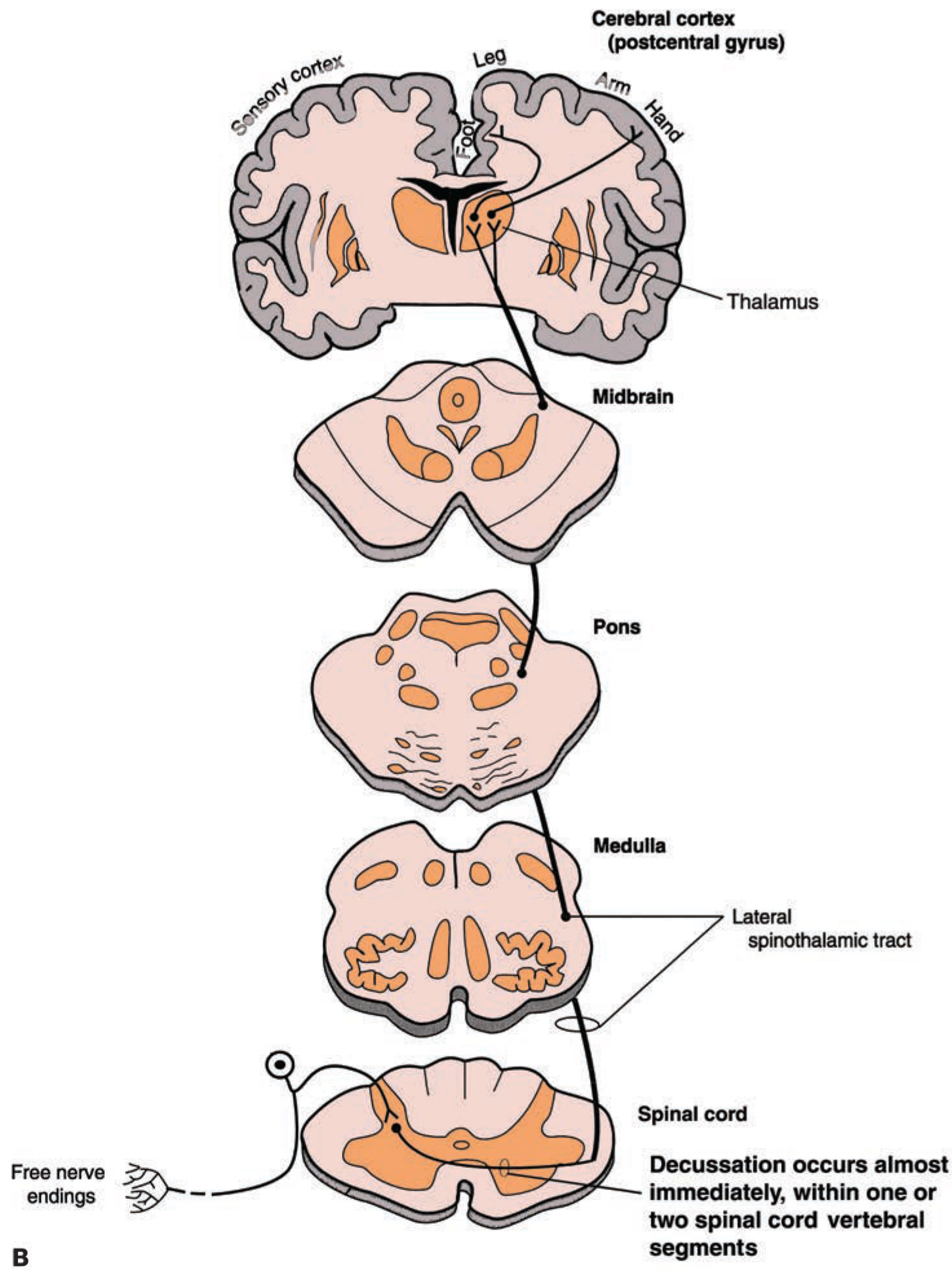
K. Muscle (Myopathy)

1. Myopathy refers to acquired disease (dystrophy to inherited conditions).
2. Symmetric weakness affects proximal muscles more than distal muscles (shoulders and hip muscles).
3. Presents with normal reflexes, but these may diminish late in the disease in comparison to muscle weakness.
4. **Normal sensation,** no fasciculations.
5. Muscle atrophy may occur late due to disuse (in contrast to rapid atrophy in motor neuron disease).


Postcentral gyrus
Somesthetic cortex
Leg area
Trunk area
Arm area
Head area
Face area
Thalamus
Medial lemniscus
Midbrain
Medial lemniscus
Pons
Medulla
Medial lemniscus
Decussation of medial lemniscus at the junction between the spinal cord and the brainstem



A



Cerebral cortex
(postcentral gyrus)
Sensory cortex
Leg
Foot
Arm
Hand
Thalamus
Midbrain
Pons
Medulla
Lateral
spinothalamic tract
Spinal cord
Free nerve
endings
Decussation occurs almost
immediately, within one or
two spinal cord vertebral
segments
B

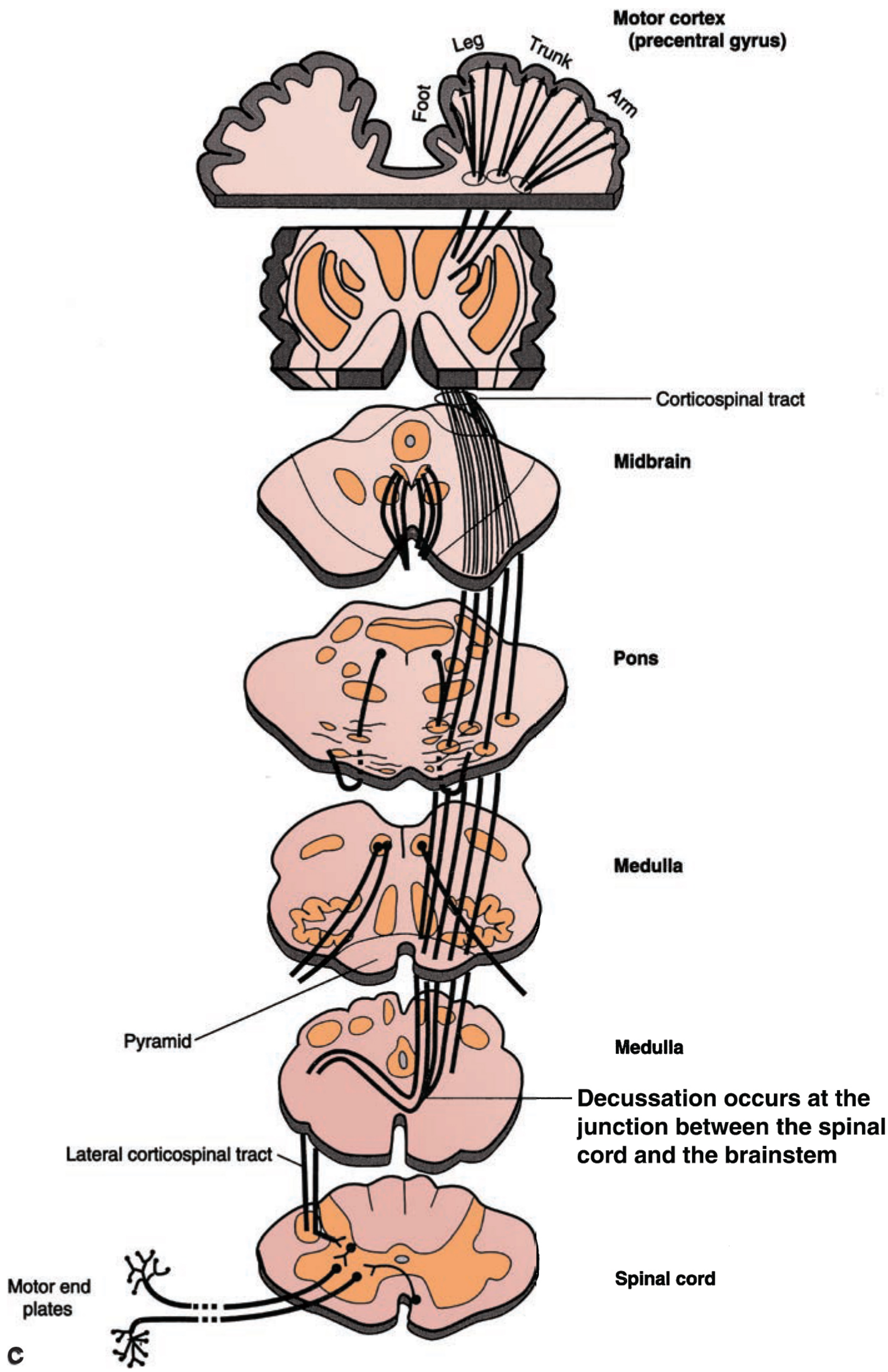


FIGURE 5-7 A: Dorsal column–medial lemniscus pathway.

(**A** reprinted with permission from Fix JD. *High-Yield Neuroanatomy*. 2nd ed. Lippincott Williams & Wilkins; 2000:39. Figure 7-2.)

B: The lateral spinothalamic tract.

(**B** reprinted with permission from Fix JD. *High-Yield Neuroanatomy*. 2nd ed. Lippincott Williams & Wilkins; 2000:41. Figure 7-3.)

C: The lateral and ventral corticospinal (pyramidal) tracts.

(**C** reprinted with permission from Fix JD. *High-Yield Neuroanatomy*. 2nd ed. Lippincott Williams & Wilkins; 2000:42. Figure 7-4.)

A 46-year-old man presents with numbness in his distal fingertips. The patient rarely seeks medical attention and has an insignificant past medical and family history. The patient reports drinking 6 to 7 beers per week and smoking a half pack of cigarettes per day. During neurologic examination, the patient is asked to extend his arms with his eyes shut and maintain his palms facing up. During this maneuver, the patient's arms both pronate.

Based on the above finding, which of the following is impaired in this patient?

A. Proprioception
B. Upper motor neuron pathway
C. Tactile sensation
D. Cerebellar function

- **The answer is B: Upper motor neuron pathway.** This patient is exhibiting pronator drift on neurologic examination. This is both a *specific* and *sensitive* test for upper motor neuron (UMN) disease. UMN disease will very often cause a weakness in supination that allows the pronating muscles to become more dominant. Therefore, when patients are asked to close their eyes and stretch out their arms with their palms facing upward, the affected arm(s) will pronate. **(A)** Proprioception can be assessed in various physical examination maneuvers. One of the more common ways to evaluate proprioception is with the Romberg test in which the patient stands with their feet together and the practitioner observes if the patient is able to maintain balance with their eyes closed. Patients with impaired proprioception will lose their balance. **(C)** Although this patient presents with "numbness," which might lead the reader to the false conclusion that he has peripheral neuropathy leading to impaired tactile sensation (measured by pinprick discrimination), this maneuver was not explicated in the question. **(D)** Cerebellar

function is responsible for balance and coordination and can be assessed by testing for rapidly alternating movements.

Connective Tissue and Joint Diseases 6

Mark Duncan

Connective Tissue Diseases

Systemic Lupus Erythematosus

A. General Characteristics

1. An autoimmune disorder leading to inflammation and tissue damage in multiple organ systems
2. Systemic lupus erythematosus (SLE) is an idiopathic chronic inflammatory disease with **genetic, environmental,** and **hormonal** factors
3. The pathophysiology involves autoantibody production, deposition of immune complexes, complement activation, and accompanying tissue destruction/vasculitis
4. Types
   a. Spontaneous SLE
   b. Cutaneous lupus erythematosus (skin lesions without systemic disease)
   c. Drug-induced lupus
   d. ANA-negative lupus—associated findings
      - Arthritis, Raynaud phenomenon, subacute cutaneous lupus
      - Serology: Ro (anti-SS-A) or antiphospholipid antibody positive, ANA negative
      - Risk of neonatal lupus in infants of affected women
      - ANA negativity can be influenced by laboratory testing methods, disease duration, and treatment

Quick HIT

Epidemiology of SLE

- **Women** of childbearing age account for 90% of cases, but men have more severe disease.
- **African American patients** are more frequently affected than Caucasian patients.
- Milder in elderly patients; more severe in children.
- Usually appears in late childhood or adolescence.

Quick HIT

Clinical Findings Associated With *Neonatal Lupus*

- Skin lesions
- Cardiac abnormalities (AV block, transposition of the great vessels)
- Valvular and septal defects

B. Clinical Features

1. Constitutional symptoms: Fatigue, malaise, fever, weight loss
2. Cutaneous: Butterfly rash (erythematous rash over cheeks and bridge of nose—found in one-third of patients) (Figure 6-1), photosensitivity, discoid lesions (erythematous raised patches with keratotic scaling), oral or nasopharyngeal ulcers, alopecia, **Raynaud phenomenon** (vasospasm of small vessels when exposed to cold, usually in fingers—found in about 20% of cases)
3. Musculoskeletal: Arthralgias (may be the first symptom of the disease—found in 90% of patients), arthritis (inflammatory and symmetric, rarely deforming as in rheumatoid arthritis [RA]), myalgia with or without myositis
4. Cardiac: Pericarditis, endocarditis (**Libman–Sacks endocarditis** is a serious complication), myocarditis
5. Pulmonary: Pleuritis (most common pulmonary finding), pleural effusion, pneumonitis (may lead to fibrosis), pulmonary HTN (rare)
6. Hematologic: Hemolytic anemia with anemia or reticulocytosis of chronic disease, leukopenia, lymphopenia, thrombocytopenia

7. Renal: Proteinuria >0.5 g/day (may have nephrotic syndrome), cellular casts, glomerulonephritis (may have hematuria), azotemia, pyuria, uremia, HTN
8. Immunologic: Impaired immune response due to many factors, including autoantibodies to lymphocytes, abnormal T-cell function, and immunosuppressive medications; often associated with antiphospholipid syndrome
9. GI: Nausea/vomiting, dyspepsia, dysphagia, peptic ulcer disease
10. CNS: Seizures, psychosis (may be subtle), depression, headaches, TIA, cerebrovascular accident
11. Other findings include conjunctivitis and an increased incidence of Raynaud phenomenon and Sjögren syndrome

Quick HIT

Clinical Course of SLE

- A chronic disease characterized by exacerbations and remissions
- Malar rash, joint pain, and fatigue are the most common initial findings. With more advanced disease, renal, pulmonary, cardiovascular, and nervous systems are affected.

FIGURE 6-1 **SLE butterfly rash.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 25.24.)

C. Diagnosis

1. Diagnosis is based on a combination of clinical and laboratory findings. Several diagnostic criteria have been used, including the 1997 ACR criteria, the 2012 SLICC criteria, and the 2019 EULAR/ACR classification criteria. In real world practice, the 2019 EULAR/ACR criteria may be less sensitive than the 1997 ACR or 2012 SLICC criteria.
   a. 2012 SLICC criteria: The patient must have at least four criteria (at least one clinical criteria and one immunologic criteria) OR biopsy-proven lupus nephritis with a positive ANA or anti-dsDNA.
2. Autoantibodies in lupus:
   a. **ANA:** Sensitive but not specific; almost all patients with SLE have elevated serum ANA levels (see Clinical Pearl 6-1, Figure 6-2, and Table 6-1)
   b. Anti-ds DNA (in 70%): very specific (but not sensitive)
   c. Anti-Smith (in 30%): very specific (but not sensitive) (see Table 6-2)
   d. Antiphospholipid antibody positivity, as determined by positive lupus anticoagulant, false-positive RPR, medium- or high-titer anticardiolipin antibody level, or positive anti–β-2 glycoprotein (see Clinical Pearl 6-2)
   e. **Antihistone Abs** (in 70%) are present in >95% of cases of **drug-induced lupus** (see Clinical Pearl 6-3). If negative, drug-induced lupus can be excluded
   f. **Ro (SS-A)** and **La (SS-B)** are found in 15% to 35%. Associated with:
      - Sjögren syndrome
      - Subacute cutaneous SLE
      - Neonatal lupus (with congenital heart block)
      - Complement deficiency (C2 and C4)
      - ANA-negative lupus

CLINICAL PEARL 6-1

Useful Criteria for Diagnosing SLE

2012 SLICC Criteria:

Clinical criteria, in the absence of other causes:

1. Acute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral or nasal ulcers
4. Nonscarring alopecia
5. Synovitis involving two or more joints
6. Serositis
7. Renal: urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500-mg protein over 24 hours OR red blood cell casts
8. Neurologic
9. Hemolytic anemia
10. Leukopenia or lymphopenia
11. Thrombocytopenia

Immunologic criteria:

1. ANA
2. Anti-ds DNA
3. Anti-Smith
4. Antiphospholipid antibody positivity
5. Low complement (C3, C4, CH50)
6. Coombs positivity (in absence of hemolytic anemia)

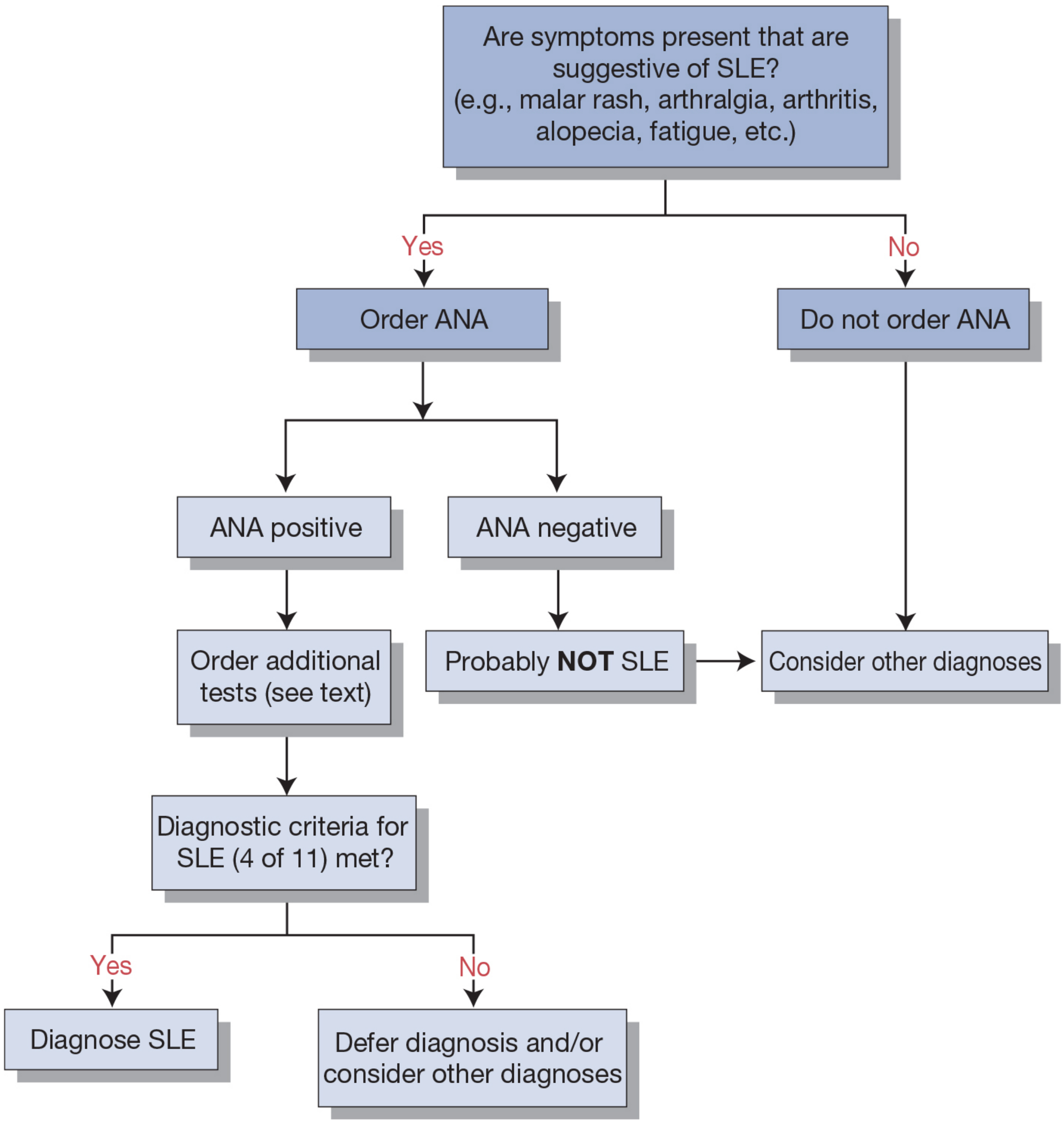


FIGURE 6-2 Diagnosis of SLE.
(Adapted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:1387. Figure 178-3.)

3. Disease activity: while some labs are helpful in the diagnosis of lupus, the following are helpful to identify disease activity:
   a. Anti-ds DNA titer
   b. Complement levels (C3, C4)
   c. ESR and CRP (acute phase reactants)
   d. Other common labs include CBC (cytopenias), UA (to evaluate active renal disease, such as pyuria, hematuria, proteinuria, casts)

Quick HIT

Conditions in Which ANAs Are Elevated

- SLE
- RA
- Scleroderma
- Sjögren syndrome
- Mixed connective tissue disease
- Polymyositis and dermatomyositis
- Drug-induced lupus

D. Treatment

1. Preventive treatment: avoid sun exposure, smoking cessation, vaccines, diet and exercise.
2. All patients with any active disease should receive hydroxychloroquine—for constitutional, cutaneous, and articular manifestations. **Hydroxychloroquine** is continued as a preventative measure even after resolution of symptoms. Baseline and subsequent annual eye examinations are needed because of **retinal toxicity.**

TABLE 6-1 Common Laboratory Markers in Rheumatologic Diseases

Laboratory Marker	Conditions	Comments
ANAs	• SLE (almost all patients) • Scleroderma • Sjögren syndrome • Polymyositis	Highly sensitive for SLE but not for the others
RF	• RA (70% of patients) • Healthy populations (up to 3%)	Neither sensitive nor specific for RA
C-ANCA	GPA	Sensitive and specific Can vary with disease activity
P-ANCA	Polyarteritis nodosa	70–80% sensitive for microscopic PAN Not specific
Lupus anticoagulant	Antiphospholipid syndrome	
ESR	• Infection (acute or chronic) • Malignancy • Rheumatologic diseases • Miscellaneous (tissue necrosis, pregnancy)	• Low sensitivity and specificity • Major uses: Diagnose/rule out inflammatory process and monitor course of inflammatory conditions
C-reactive protein	• Inflammatory states and infection • Miscellaneous conditions (e.g., MI, vasculitis, trauma, malignancy, pancreatitis)	• Primarily used for infection—much more sensitive and specific than ESR • If levels are markedly elevated (>15), bacterial infection is likely present

TABLE 6-2 HLA Associations With Rheumatic Diseases

Disease	Associated HLA
SLE	HLA-DR2 and HLA-DR3
Sjögren syndrome	HLA-DR3
RA	HLA-DR4
Ankylosing spondylitis, Reiter syndrome, psoriatic arthritis	HLA-B27

CLINICAL PEARL 6-2

Antiphospholipid Antibody Syndrome

- A hypercoagulable state that can be idiopathic or associated with SLE (or other collagen vascular diseases such as scleroderma)
  - Typical findings
  - Recurrent venous thrombosis—pulmonary embolism is a risk
  - Recurrent arterial thrombosis
  - Recurrent fetal loss (abortions)
  - Thrombocytopenia
  - Livedo reticularis
  - Laboratory findings: Presence of lupus anticoagulant, anticardiolipin antibody, or both. Prolonged PTT or PT is not corrected by adding normal plasma
  - Treatment is long-term anticoagulation (INR of 2.5 to 3.5)
  - APA antibodies react with cardiolipin, a reagent in VDRL and RPR tests leading to false positives

CLINICAL PEARL 6-3

Drug-Induced Lupus

- Certain drugs may produce a lupus-like syndrome that is similar to SLE except that it **does not affect the CNS or kidneys**.
- If renal or CNS involvement is present, it is **not** drug-induced lupus. In addition, the classic butterfly rash, alopecia, and ulcers are typically not seen in drug-induced lupus.
- Most patients improve after withdrawal of the offending drug. Therefore, the prognosis is obviously more favorable.
- Commonly implicated agents include hydralazine, procainamide, isoniazid, chlorpromazine, methyldopa, and quinidine.
- Laboratory findings in drug-induced lupus: **Antihistone antibodies** are always present; there is an absence of anti-ds DNA and anti-Sm Ab.

3. Mild active disease: NSAIDs or low-dose steroids.
4. Moderate or severe disease typically requires a steroid-sparing immunosuppressive agent.
5. Severe organ- or life-threatening flares should be treated with high-dose steroids and other immunosuppressive agents (azathioprine, mycophenolate, cyclophosphamide, etc.).
6. Many other treatment options are specific to the organ and manifestation of disease. For example, cutaneous lupus is treated very differently than lupus nephritis.

Quick HIT

Steroids are the initial treatment for SLE patients with acute flare.
Hydroxychloroquine for long-term treatment for SLE can cause retinal toxicity.

Quick HIT

RA is unlikely if:

- Joint distribution is not symmetric OR
- DIPs are involved OR
- Morning stiffness is absent

Rheumatoid Arthritis

A. General Characteristics

1. RA is a chronic **inflammatory** autoimmune disease involving the **synovium of joints.** The inflamed synovium can cause damage to cartilage and bone.
2. It is a systemic disease that has many extra-articular manifestations (see below).
3. The usual age of onset is 20 to 40 years; it is more common in women than in men (3:1).
4. Etiology is uncertain, but risk of RA is multifactorial. HLA-DRB1 is the strongest genetic risk factor, and smoking is the strongest environmental risk factor.

> ***Quick* HIT**
>
> Much of the joint damage that ultimately leads to disability occurs early in disease, so early treatment with DMARDs is critical.

B. Clinical Features

1. Inflammatory polyarthritis that is most often a progressive disease, though some patients may have intermittent symptoms without severe progression (Figure 6-3)
   a. **Morning stiffness** lasting >1 hour—improves as the day progresses
   b. Joints commonly involved include **joints of the hands (PIP, MCP) and wrists,** knees, ankles, elbows, hips, and shoulders
   c. Characteristic hand deformities
      - Ulnar deviation of the MCP joints (Figure 6-4A)
      - *Boutonnière deformities* of the PIP joints (PIP flexed, DIP hyperextended) (Figure 6-4)
      - *Swan-neck contractures* of the fingers (MCP flexed, PIP hyperextended, DIP flexed) (Figure 6-4B)
2. Extra-articular manifestations (see Table 6-3)
   a. Low-grade fever, weight loss
   b. Fatigue can be prominent because this is a systemic disease

3. Cervical spine involvement is common at **C1–C2 (subluxation and instability)**, but it is less common in the lower cervical spine
   a. Instability of the cervical spine is a potentially life-threatening complication of RA. Most patients do not have neurologic involvement, but if they do, it can be progressive and fatal if not treated surgically.
   b. This is seen in 30% to 40% of patients. All patients with RA should have cervical spine **radiographs before undergoing any surgery** (due to risk of neurologic injury during intubation). However, disease-modifying antirheumatic drugs (DMARDs) have dramatically reduced the need for cervical spine surgery in RA patients.
4. Subcutaneous **rheumatoid nodules** over extensor surfaces may also occur in visceral structures—for example, lungs, pleura, pericardium (Figure 6-5)
   a. Pathognomonic for RA
   b. Nearly always occurs in seropositive patients (i.e., those with RF)

***Quick* HIT**

Poor Prognostic Indicators in RA

- High RF titers
- Subcutaneous nodules
- Erosive arthritis

***Quick* HIT**

In RA, changes in joints are usually more extensive than in OA because the entire synovium is involved in RA. Note that osteophytes (characteristic of OA) are not present in RA.

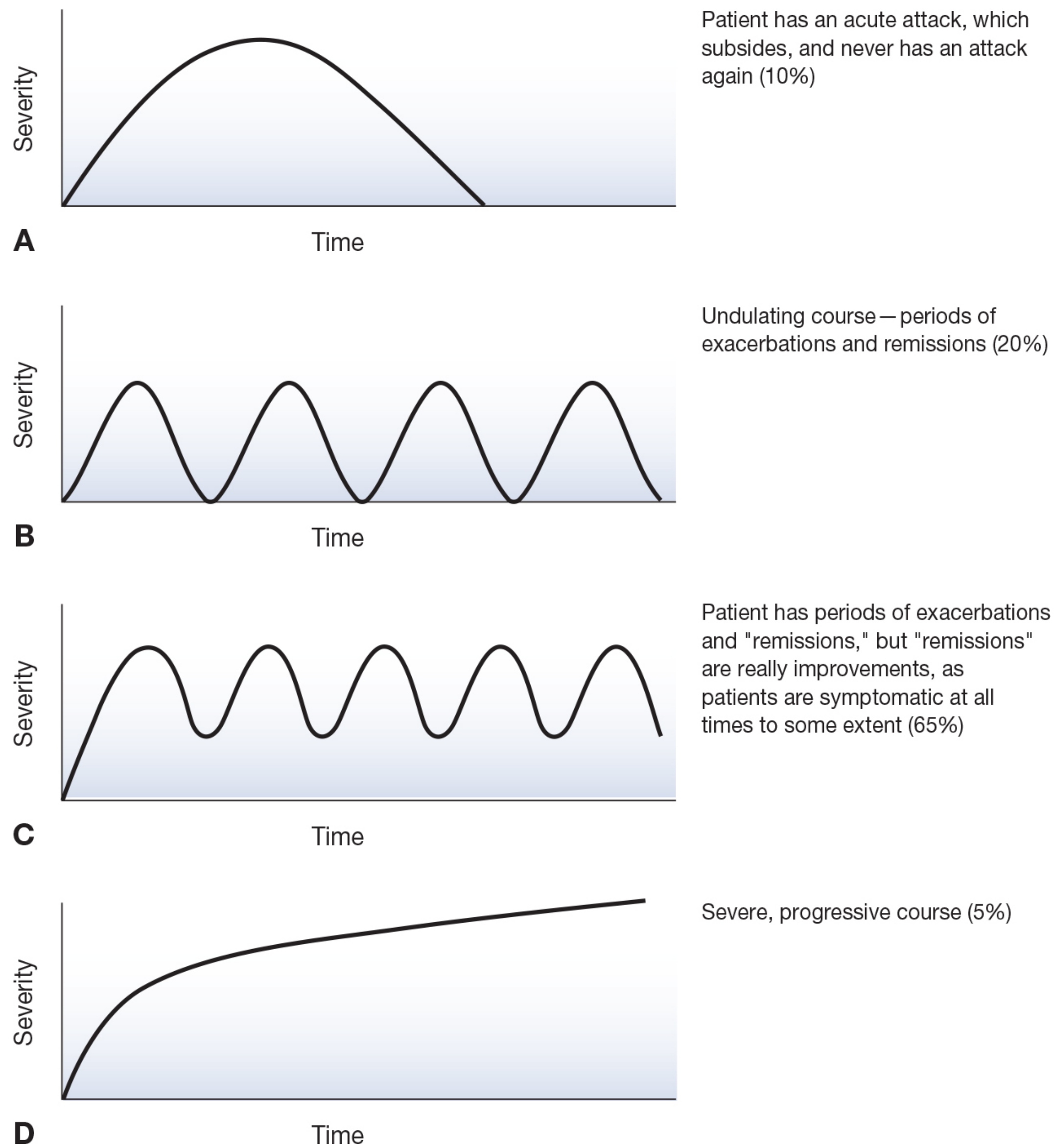


FIGURE 6-3 **The clinical course of RA can be grouped into four classes of patients.**

A B

FIGURE 6-4 **Ulnar deviation of the MCP joints.**
(**A** reprinted with permission from Harris JH, Harris WH, Novelline RA. *The Radiology of Emergency Medicine*. 3rd ed. Williams & Wilkins; 1993:440. **B** reprinted with permission from Smeltzer SC, Bare BG. *Brunner and Suddarth's Textbook of Medical-Surgical Nursing*. 10th ed. Lippincott Williams & Wilkins; 2003. Figure 54-4B.)

TABLE 6-3 Extra-articular Manifestations in Rheumatoid Arthritis

Constitutional Symptoms	Malaise, Anorexia, Some Weight Loss, Fever
Cutaneous	• Skin becomes thin and atrophic and bruises easily • Vasculitic changes/ulcerations involving fingers, nail folds • Subcutaneous **rheumatoid nodules** (elbows, sacrum, occiput)—**pathognomonic for RA**
Pulmonary	• Pleural effusions (very common)—**pleural fluid characteristically has very low glucose** and low complement • Pulmonary fibrosis—with a restrictive pattern on pulmonary function tests and a honeycomb pattern on CXR • Pulmonary infiltrates • Rheumatic nodules in lungs (similar to those on skin)—can cavitate or become infected
Cardiac	• Rheumatic nodules in heart—can lead to conduction disturbances (heart block and bundle branch block) • Pericarditis—in 40% of patients with RA • Pericardial effusion
Eyes	• Scleritis • Scleromalacia—softening of the sclera; if not treated may perforate, leading to blindness • Dry eyes (and dry mucous membranes in general); may develop Sjögren syndrome
Nervous System	Mononeuritis multiplex—infarction of nerve trunk. Implies systemic vasculitis, which is a bad sign
Felty Syndrome	• Triad of RA, neutropenia, and splenomegaly • Also anemia, thrombocytopenia, and lymphadenopathy • Associated with high titers of RF and extra-articular disease • Increased susceptibility to infection • Usually occurs fairly late in the disease process
Blood	• Anemia of chronic disease: Mild, normocytic, normochromic anemia • Thrombocytosis
Vasculitis	A microvascular vasculitis—can progress to mesenteric vasculitis, PAN, or other vascular syndromes

C. Diagnosis

1. The 2010 ACR/EULAR criteria are based on joint involvement, positive serologies and elevated inflammatory markers, and chronicity
2. Serology
   a. Rheumatoid factor (RF) is sensitive but not specific for RA. RF is eventually present in 80% of patients with RA (may be absent early in the disease), but is also present in up to 3% of the healthy population
      - RF titers rarely change with disease activity and are not useful for following patients.
      - Helpful in determining prognosis. High titers → more severe disease
   b. Anticitrullinated peptide/protein antibodies (ACPA)—sensitivity is 50% to 75%, specificity is over 90%

> **Quick HIT**
>
> Patients with diagnosis of RA who have a positive RF, ACPA, or both are at a higher risk of developing erosive joint damage—early treatment with DMARDs is indicated.

3. Radiographs (Figure 6-6). Not required for a diagnosis of RA but may have the following characteristic findings
   a. Loss of juxta-articular bone mass (periarticular osteoporosis) near the finger joints
   b. **Narrowing of the joint space** (due to thinning of the articular cartilage) is usually seen late in the disease
   c. **Bony erosions** at the margins of the joint
4. Synovial fluid analysis (see Table 6-4)

FIGURE 6-5 **Rheumatoid nodules of the hand.**
(Reprinted with permission from Stedman TL. *Stedman's Medical Dictionary for the Health Professions and Nursing: Illustrated*. 6th ed. Lippincott Williams & Wilkins; 2007.)

A B

FIGURE 6-6 Posteroanterior radiographs of the hand showing the typical pattern of involvement for (A) osteoarthritis (osteophytes, subchondral sclerosis, joint space narrowing) (*arrows*) and (B) rheumatoid arthritis (periarticular erosions, osteopenia) (*arrows*).

(**A** and **B** reprinted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:1463. Figures 190.4A and B.)

TABLE 6-4 Synovial Fluid Analysis

Condition	Appearance of Fluid	WBC/mm^3	PMNs	Other Findings
Normal	Clear	<200	<25%	
Noninflammatory arthritis (OA/trauma)	Clear, yellow: Possibly red if traumatic	<2,000	<25%	RBCs if traumatic
Inflammatory arthritis (RA, gout, pseudogout, Reiter syndrome)	Cloudy yellow	>5,000	50–70%	Positively birefringent crystals with pseudogout; negatively birefringent crystals with gout
Septic arthritis (bacterial, tuberculosis)	Turbid, purulent	Usually >50,000	>70%	Synovial fluid culture positive for most cases of bacterial arthritis, except gonococcal (only 25% are positive)

Quick HIT

Variants of RA

- **Felty syndrome:** anemia, neutropenia, splenomegaly, and RA.
- **Juvenile RA:** begins before 18 years of age. Extra-articular manifestations may predominate (Still disease) or arthritis may predominate.
- **Caplan syndrome:** RA associated with pneumoconiosis.

Quick HIT

Combination therapy with first-line drugs (methotrexate, hydroxychloroquine, and sulfasalazine) produces higher remission rates.

Quick HIT

Radiographs have become less important in diagnosis of RA, as joint abnormalities occur very late. DMARDs started well before radiographs indicate abnormality.

Quick HIT

Methotrexate is the initial treatment for RA.

D. Treatment

1. Goal is to minimize pain and swelling, prevent disease progression, and help patient remain as functional as possible
2. Exercise helps to maintain range of motion and muscle strength
3. Symptomatic treatment
   a. NSAIDs are the drugs of choice for pain control
   b. Corticosteroids (low dose)—use these if NSAIDs do not provide adequate relief. Short-term treatment may be appropriate but avoid long-term use
4. DMARDs
   a. General principles
      - Can reduce morbidity and mortality (by nearly 30%)—by limiting complications, slowing progression of disease, and preserving joint function
      - **Should be initiated early** (at the time of diagnosis)
      - They have a slow onset of action (6 weeks or longer for effect to be seen), so begin treating RA while waiting for the disease-modifying therapy to take effect. Gradually taper and discontinue NSAIDs and corticosteroids once effects are evident

   b. Methotrexate—best initial DMARD
      - Initial improvement is seen in 4 to 6 weeks
      - Side effects include GI upset, oral ulcers (stomatitis), mild alopecia, **bone marrow suppression** (reduced with folic acid supplementation), hepatocellular injury, and idiosyncratic interstitial pneumonitis, which may lead to pulmonary fibrosis. It increases liver enzymes in some patients
      - Closely monitor liver and renal function

   c. Alternatives: leflunomide, sulfasalazine, hydroxychloroquine, TNF inhibitors
   d. Non-TNF biologics (baricitinibb, tofacitinib, others) are also options if disease activity remains high despite methotrexate

5. Surgery (in severe cases)
   a. Synovectomy (arthroscopic) decreases joint pain and swelling but does not prevent x-ray progression and does not improve joint range of motion
   b. Joint replacement surgery for severe pain unresponsive to conservative measures

A 39-year-old woman with a history of rheumatoid arthritis presents for routine care. The patient's symptoms are well controlled on her current medication regimen. Routine laboratory values reveal the following.

Hemoglobin	9.8 g/dL
Mean corpuscular volume (MCV)	110 fL
Leukocyte count	9,500/mm^3
Platelets	280,000/mm^3

Which of the following is this patient taking for her rheumatoid arthritis?

A. Methotrexate
B. Cyclosporine
C. Corticosteroids
D. Hydroxychloroquine

- **The answer is A: Methotrexate.** The patient in this question has rheumatoid arthritis and is presenting with a macrocytic anemia (MCV >100 fL). Of the four choices, only methotrexate can cause a macrocytic anemia. Methotrexate is a disease-modifying antirheumatic drug (DMARD), which inhibits the metabolism of folic acid by inhibiting dihydrofolate reductase. Other important side effects include stomatitis, lung fibrosis, rash, and pancytopenia. Therefore, patients on methotrexate need to have their blood counts (CBC) checked every 3 months. **(B)** Cyclosporine is an immunosuppressant drug used commonly after organ transplantation. It is associated with increased viral infection, nephrotoxicity, hypomagnesemia, and hepatotoxicity. **(C)** Corticosteroids are used in the treatment of rheumatoid arthritis (RA) and side effects include osteoporosis, impaired wound healing, and other effects seen in Cushing syndrome. **(D)** Hydroxychloroquine is also a DMARD used

in the treatment of RA, but its side effects include visual problems and hemolytic anemia found in G6PD deficiency.

Systemic Sclerosis (Scleroderma)

A. General Characteristics

1. A chronic connective tissue disorder that can lead to widespread fibrosis
2. Pathophysiology: Cytokines stimulate fibroblasts, causing an abnormal amount of collagen deposition. It is the high **quantity** of collagen that causes the problems associated with this disease (composition of the collagen is normal)
3. Scleroderma is more common in women. Average age of onset is 35 to 50 years
4. There are two types of scleroderma: Diffuse (20%) and limited (80%) (see Table 6-5)

> ***Quick* HIT**
>
> The most common causes of death in SLE are opportunistic infections, renal failure, and cardiovascular disease.

> ***Quick* HIT**
>
> Only **diffuse scleroderma** form has renal, lung, and heart involvement.

B. Clinical Features

1. Raynaud phenomenon
   a. Present in almost all patients; usually appears before other findings
   b. Caused by vasospasm and thickening of vessel walls in the digits
   c. Can lead to digital ischemia, with ulceration and infarction/gangrene
   d. Cold temperature and stress bring about color changes of fingers—blanching first, then cyanotic, and then red from reactive hyperemia

TABLE 6-5 Diffuse Versus Limited Scleroderma

Diffuse	Limited
Widespread skin involvement	Skin involvement limited to distal extremities (and face, neck)—sparing of the trunk
Rapid onset of symptoms (skin and other complications occur rapidly after onset of Raynaud phenomenon)	Delayed onset: Skin involvement occurs slowly after the onset of Raynaud phenomenon
Significant visceral involvement (i.e., fibrosis of internal organs)—lung, heart, GI tract, kidneys	Visceral involvement occurs late—pulmonary HTN and ischemic vascular disease; minimal constitutional symptoms
Antitopoisomerase I (antiscleroderma-70) antibody	Anticentromere antibody
Poorer prognosis—10-yr survival is 40–65% • Peripheral edema (of hands and legs), polyarthritis, fatigue, and weakness (muscle involvement), carpal tunnel syndrome • Renal failure can occur, but now rare • Interstitial lung disease more common	Better prognosis than diffuse form. Normal life span is expected in most cases, unless severe pulmonary HTN develops. CREST syndrome is a variant **C**alcinosis of the digits **R**aynaud phenomenon **E**sophageal motility dysfunction **S**clerodactyly of the fingers **T**elangiectases (over the digits and under the nails)

2. Cutaneous fibrosis
   a. Tightening of skin of the face and extremities (**sclerodactyly** refers to a claw-like appearance of the hand)
   b. Can lead to contractures, disability, and disfigurement
3. GI involvement
   a. Occurs in most patients (both diffuse and limited)
   b. Findings include dysphagia/reflux from esophageal immobility (up to 90% of patients), delayed gastric emptying, constipation/diarrhea, abdominal distention, and pseudo-obstruction. Prolonged acid reflux may eventually lead to esophageal strictures
4. Pulmonary involvement
   a. Most common cause of death from scleroderma
   b. Interstitial fibrosis and/or pulmonary HTN may also be present

5. Cardiac involvement: pericardial effusions, myocardial involvement that can lead to CHF, arrhythmias
6. Renal involvement (renal crisis—rapid malignant hypertension) occurs in patients with diffuse disease (rare today)

Quick HIT

Differential Diagnosis of Raynaud Phenomenon
- Primary—no other disorder exists
- Scleroderma
- SLE
- Mixed connective tissue disease
- Vasculitis (e.g., thromboangiitis obliterans)
- Certain medications (e.g., β-blockers, nicotine, bleomycin)

Quick HIT

The **degree of skin involvement** predicts prognosis: Diffuse scleroderma has a worse prognosis than limited scleroderma.

C. Diagnosis

1. Diagnostic tests are of limited utility. Almost all patients have elevated ANAs (high sensitivity, low specificity).
2. **Anticentromere antibody** is very specific for the limited form.
3. **Antitopoisomerase I** (antiscleroderma-70) Ab is very specific for the diffuse form.
4. **Anti-RNA polymerase III antibody is seen in diffuse cutaneous systemic sclerosis**
5. Barium swallow (esophageal dysmotility) and pulmonary function test are used to detect complications.

D. Treatment

1. Treatment is tailored to the organ involved
2. Early treatment with systemic immunosuppression can slow the progression of systemic sclerosis and its complications
3. NSAIDs for musculoskeletal pains

4. H_2-Blockers or proton pump inhibitors for esophageal reflux
5. Raynaud phenomenon—avoid cold and smoking, keep hands warm; if severe, use calcium channel blockers
6. ACE inhibitors are used to prevent and treat renal hypertensive crisis

A 37-year-old woman presents with progressive shortness of breath. The patient also reports painful joints over the past 5 months, especially in her fingers. She has a past medical history of GERD, which is controlled with omeprazole. On physical examination, the patient has thickened skin over the acral surfaces. Examination reveals skin tightening around her mouth and fingers.

Which of the following will likely be positive in this patient?

A. Antihistone antibodies
B. RF
C. Antitopoisomerase antibodies
D. Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA)

- **The answer is C: Antitopoisomerase antibodies.** This patient likely has a diagnosis of systemic sclerosis, an autoimmune and connective tissue disease that is characterized by thickening of the skin from accumulation of collagen. This patient is presenting with lung findings and therefore likely has the *diffuse* form of systemic sclerosis. This condition is characterized by the presence of anti Scl-70 antibodies (also called *antitopoisomerase I* antibodies). **(A)** Antihistone antibodies are found in drug-induced lupus. Medications that are most likely responsible include hydralazine, procainamide, and isoniazid. **(B)** Rheumatoid factor (RF) is often found in rheumatoid arthritis but can also be found in other autoimmune diseases. **(D)** Positive c-ANCA is found in granulomatosis with polyangiitis.

Sjögren Syndrome

A. General Characteristics

1. Sjögren syndrome is an autoimmune disease most common in women. Lymphocytes infiltrate and destroy the lacrimal and salivary glands
2. A multiorgan disease (can also involve the skin, lungs, thyroid, vessels, and liver)
3. Primary versus secondary Sjögren syndrome
   a. Primary Sjögren syndrome: Dry eyes and dry mouth, along with lymphocytic infiltration of the minor salivary glands (on histology); patients do not have another rheumatologic disease
   b. Secondary Sjögren syndrome: Dry eyes and dry mouth along with a **connective tissue disease** (RA, systemic sclerosis, SLE, polymyositis)
4. Patients have increased risk of non-Hodgkin lymphoma. Malignancy is the most common cause of death

Quick HIT

- Twenty percent of patients with scleroderma have Sjögren syndrome.
- In patients with Sjögren syndrome, search for **occult lymphoma** (look for lymphadenopathy and hepatosplenomegaly).

B. Clinical Features

1. Dry eyes—burning, redness, blurred vision, keratoconjunctivitis sicca
2. Dry mouth and tooth decay
3. Arthralgias, arthritis, fatigue
4. Interstitial nephritis and vasculitis

C. Diagnosis

1. ANAs are present in 95% of patients. RF is present in 50% to 75% of patients with secondary disease.
2. **Ro (SS-A)** is present in 60% of patients, and **La (SS-B)** (more specific) is present in 40% of patients.

3. **Schirmer test:** Filter paper inserted in eye to measure lacrimal gland output (degree of wetting in a specified time period)—high sensitivity and specificity.
4. Salivary gland biopsy (lip or parotid) is the most accurate but not needed for diagnosis.

Quick HIT

Patients with antibodies to Ro (SS-A) are at increased risk of having a child with neonatal SLE (with congenital heart block).

D. Treatment

1. Pilocarpine or cevimeline (muscarinic agonists that enhance oral and ocular secretions)
2. Artificial tears for dry eyes
3. Good oral hygiene
4. NSAIDs, steroids for arthralgias, arthritis
5. Patients with secondary Sjögren syndrome—therapy for connective tissue disease

Mixed Connective Tissue Disease

- Mixed connective tissue disease is an "overlap" syndrome with clinical features similar to those of SLE, RA, systemic sclerosis, and polymyositis. Findings consistent with each of these diseases do not necessarily occur simultaneously. It usually takes some time for a pattern to be identified and a diagnosis of mixed connective tissue disease to be made.
- Clinical findings include pulmonary involvement, esophageal dysfunction, polyarthritis, sclerodactyly, cutaneous manifestations, myopathy, and Raynaud phenomenon.
- The presence of **anti–U1-RNP Abs** is a key laboratory finding. High ANA and RF may be present.
- Treatment varies according to which specific disease predominates.

Crystal-Induced Arthritides

Gout

A. General Characteristics

1. Gout is an inflammatory monoarticular arthritis caused by the crystallization of monosodium urate in joints (see Table 6-6). Hyperuricemia is a hallmark of the disease, but it does not by itself indicate gout
2. Ninety percent of patients are men over 30 years of age. Women are not affected until after menopause due to decreased estrogen-mediated urinary urate excretion
3. Pathogenesis
   a. Increased production of uric acid
      - Hypoxanthine-guanine phosphoribosyltransferase deficiency—for example, in Lesch–Nyhan syndrome
      - **Phosphoribosyl pyrophosphate synthetase** overactivity

   b. **Increased cell turnover** associated with several conditions, including cancer chemotherapy, chronic hemolysis, and hematologic malignancies. Decreased excretion of uric acid (accounts for 90% of cases)
      - Renal disease
      - NSAIDs, diuretics
      - Acidosis
4. Pathophysiology of inflammation
   a. PMNs play a key role in the acute inflammation of gout.
   b. It develops when uric acid crystals collect in the synovial fluid as the extracellular fluid becomes saturated with uric acid.
   c. IgGs coat monosodium urate crystals, which are phagocytized by PMNs, leading to the release of inflammatory mediators and proteolytic enzymes from the PMNs, which then result in inflammation.

B. Clinical Features

1. Asymptomatic hyperuricemia
   a. Increased serum uric acid level in the absence of clinical findings of gout, may be present without symptoms for 10 to 20 years or longer.
   b. Should not be treated because over 95% of patients remain asymptomatic.

TABLE 6-6 Major Arthritides

	Osteoarthritis	Rheumatoid Arthritis	Gouty Arthritis
Onset	Insidious	Insidious	Sudden
Common locations	Weight-bearing joints (knees, hips, lumbar/cervical spine), hands	Hands (PIP, MCP), wrists, ankles, knees	Great toe, ankles, knees, elbows
Presence of inflammation	No	Yes	Yes
Radiographic changes	Narrowed joint space, osteophytes, subchondral sclerosis, subchondral cysts	Narrowed joint space, bony erosions	Punched-out erosions with overhanging rim of cortical bone
Laboratory findings	None	Elevated ESR, RF, anemia	Crystals
Other features	• No systemic findings • Bouchard nodes and Heberden nodes in hands	• Systemic findings—extra-articular manifestations common • Ulnar deviation, swan-neck, and boutonnière deformity	• Tophi • Nephrolithiasis

2. Acute gout flare
   a. Peak age of onset is 40 to 60 years of age for men.
   b. Initial attack usually involves sudden onset of exquisite pain. Pain often wakes the patient from sleep.
      - Most often affects the big toe—the first metatarsophalangeal joint **(podagra)**. Other common joints affected are ankles and knees.

c. Pain, erythema, swelling, tenderness, and warmth.
d. Fever may or may not be present.
e. As it resolves, the patient may have desquamation of overlying skin.

Quick HIT

Precipitants of an Acute Gouty Attack

- Diet (e.g., fatty foods, alcohol)
- Dehydration
- Trauma
- Medications (e.g., diuretics)

3. Intercritical gout
   a. An asymptomatic period after the initial attack, which is unusual after other rheumatologic disorders and thus suggests the diagnosis of gout.
   b. Sixty percent of patients have a recurrence within 1 year. Some patients (fewer than 10%) never have another attack of gout.
   c. There is a 75% likelihood of a second attack within the first 2 years.
   d. Attacks tend to become polyarticular with increased severity over time.
4. Chronic tophaceous gout
   a. Occurs in people who have had poorly controlled gout for more than 10 to 20 years
   b. Tophi
      - Aggregations of urate crystals surrounded by giant cells in an inflammatory reaction.
      - Tophi cause deformity and destruction of hard and soft tissues. In joints, they lead to destruction of cartilage and bone, triggering secondary degeneration and development of arthritis. They may be extra-articular.
   c. Common locations of tophi: Extensor surface of forearms, elbows, knees, Achilles tendons, and pinna of external ear

Quick HIT

Do a Gram stain and culture of the synovial fluid to **rule out septic arthritis,** which is the most worrisome diagnosis on the differential list.

C. Diagnosis

1. Joint aspiration and synovial fluid analysis (under a polarizing microscope) is the only way to make a definitive diagnosis—**needle-shaped and negatively birefringent urate crystals** appear in synovial fluid.
2. Serum uric acid is **not** helpful in diagnosis because it can be normal even during an acute gouty attack.
3. Radiographs reveal punched-out erosions with an overhanging rim of cortical bone in advanced disease.

Quick HIT

Complications of Gout

- Nephrolithiasis—risk is small (less than 1% per year)
- Degenerative arthritis occurs in less than 15% of patients.

D. Treatment

1. In all stages, avoid secondary causes of hyperuricemia
   a. Medications that increase uric acid levels (thiazide and loop diuretics)
   b. Obesity
   c. Reduce alcohol intake
   d. Reduce dietary purine intake, limit intake of seafood/red meat

Quick HIT

In acute gout, avoid aspirin (can aggravate the problem), acetaminophen (has no anti-inflammatory properties), and urate-lowering drugs (initiation during flare may worsen or prolong the flare). Initiate urate-lowering pharmacotherapy once the acute flare has resolved.

2. Acute gout
   a. Rest the affected joint
   b. Treatment is based on many factors, including comorbidities, and on what treatments have worked best for the patient in the past. NSAIDs, colchicine, and steroids are all acceptable first-line treatments
   c. NSAIDs
      - One of the first-line treatments for an acute gout flare (indomethacin is traditionally used, but other NSAIDs are effective)
      - Avoid in patients with history of peptic ulcer disease and GI bleed, acute or chronic kidney disease, heart failure, or cirrhosis
   d. Colchicine
      - An alternative for patients who cannot take NSAIDs or did not respond to NSAIDs.
      - High-dose treatment leads to significant GI side effects, thus lower-dose regimens are favored
      - Dose must be reduced in renal insufficiency and can cause cytopenia
   e. Corticosteroids
      - Oral prednisone (7- to 10-day taper typically)
      - Intra-articular corticosteroid injections (if only one joint is involved)—dramatic relief of symptoms
      - Avoid system steroids if concern for active infection, brittle diabetes
3. Chronic treatment
   a. Wait until patient has had at least two acute gouty attacks before initiating prophylactic therapy. This is because the second attack may take years to occur (if at all), and so the risk-to-benefit ratio for prophylactic medication is not favorable after one gouty attack. The presence of tophi is also an indication for prophylactic therapy.
   b. When giving prophylaxis, add either colchicine or an NSAID for 3 to 6 months to prevent an acute attack. The colchicine or NSAID can then be discontinued, and the patient can remain on the uricosuric agent or allopurinol indefinitely.

c. First-line therapy is typically allopurinol, though high-risk groups should be tested for HLA-B*5801 first (risk of severe hypersensitivity reactions including Stevens–Johnson syndrome and TEN). Allopurinol is a xanthine oxidase inhibitor, which decreases uric acid synthesis.
   - Uricosuric drugs (probenecid, lesinurad, sulfinpyrazone) are added if the uric acid goal is not met and if urinary urate excretion is low or normal.
   - For patients who are HLA-B*5801 positive, or cannot achieve goal uric acid levels on allopurinol, the xanthine oxidase inhibitor febuxostat is used.
   - Uricases (pegloticase, rasburicase)—These drugs **catalyze the conversion of urate into allantoin, a more soluble purine degradation product**. They cause rapid lowering of serum urate levels.

Pseudogout (Calcium Pyrophosphate Deposition Disease)

A. General Characteristics

1. Calcium pyrophosphate crystals deposit in joints, leading to inflammation.
2. Risk factors
   a. Deposition increases with age and with OA of the joints. Therefore, pseudogout is common in **elderly patients with degenerative joint disease.**
   b. Other conditions that may increase crystal deposition include **hemochromatosis, hyperparathyroidism**, hypothyroidism, and Bartter syndrome.

Quick HIT

Presentation of pseudogout is similar to gout, but typically occurs in larger joints (knee).

B. Clinical Features

1. The most common joints affected are knees and wrists.
2. It is classically monoarticular, but can be polyarticular.

C. Diagnosis

1. Joint aspirate is required for definitive diagnosis—**weakly positively birefringent, rod-shaped and rhomboidal crystals** in synovial fluid (calcium pyrophosphate crystals) (Figure 6-7)
2. Radiographs—chondrocalcinosis (cartilage calcification)

D. Treatment

1. Treat the underlying disorder (if identified)
2. Symptomatic management is similar to that for gout
   - First-line therapy includes NSAIDs
   - Colchicine is useful for prophylaxis
   - Intra-articular steroid injections, particularly with triamcinolone
3. Total joint replacement is appropriate if symptoms are debilitating

A 61-year-old man with a history of alcohol use disorder and parathyroid adenoma presents with pain in his left knee for the last 2 days. He denies fevers, chills, night sweats, or any history of trauma to the knee, but does endorse abdominal pain and constipation. Physical examination is significant for tenderness and erythematous skin overlying the left knee. There is also marked swelling of the left knee. Laboratory findings reveal an elevated calcium level (12.1 mg/dL).

If joint aspiration is performed, which of the following will be seen on synovial fluid analysis?

A. Negatively birefringent needle-shaped crystals
B. Positively birefringent rhomboid-shaped crystals
C. Neutrophil predominance with gram-positive cocci
D. Normal synovial fluid findings

- **The answer is B: Positively birefringent rhomboid-shaped crystals.** This patient has a history of parathyroid adenoma that is likely causing hypercalcemia secondary to hyperparathyroidism. Patients with hypercalcemia are at risk for developing pseudogout, a rheumatologic disease with diverse symptoms and signs arising from the accumulation of calcium pyrophosphate dihydrate crystals in the connective tissues. It commonly presents with acute onset, painful monoarthropathy of the knee. Joint aspiration with synovial fluid analysis confirms the diagnosis, showing rhomboid-shaped crystals that are positively birefringent. **(A)** Negatively birefringent needle-shaped crystals describe *gout*, which also presents with acute onset monoarthropathy, but usually affects the first metatarsophalangeal joint of the foot. Furthermore, gout is not triggered by hypercalcemia. **(C)** Neutrophil predominant synovial fluid with gram-positive cocci is diagnostic of septic arthritis. This patient has no fever, making septic arthritis highly unlikely from the clinical picture alone. **(D)** Normal synovial fluid findings are not the norm in the setting of pseudogout.

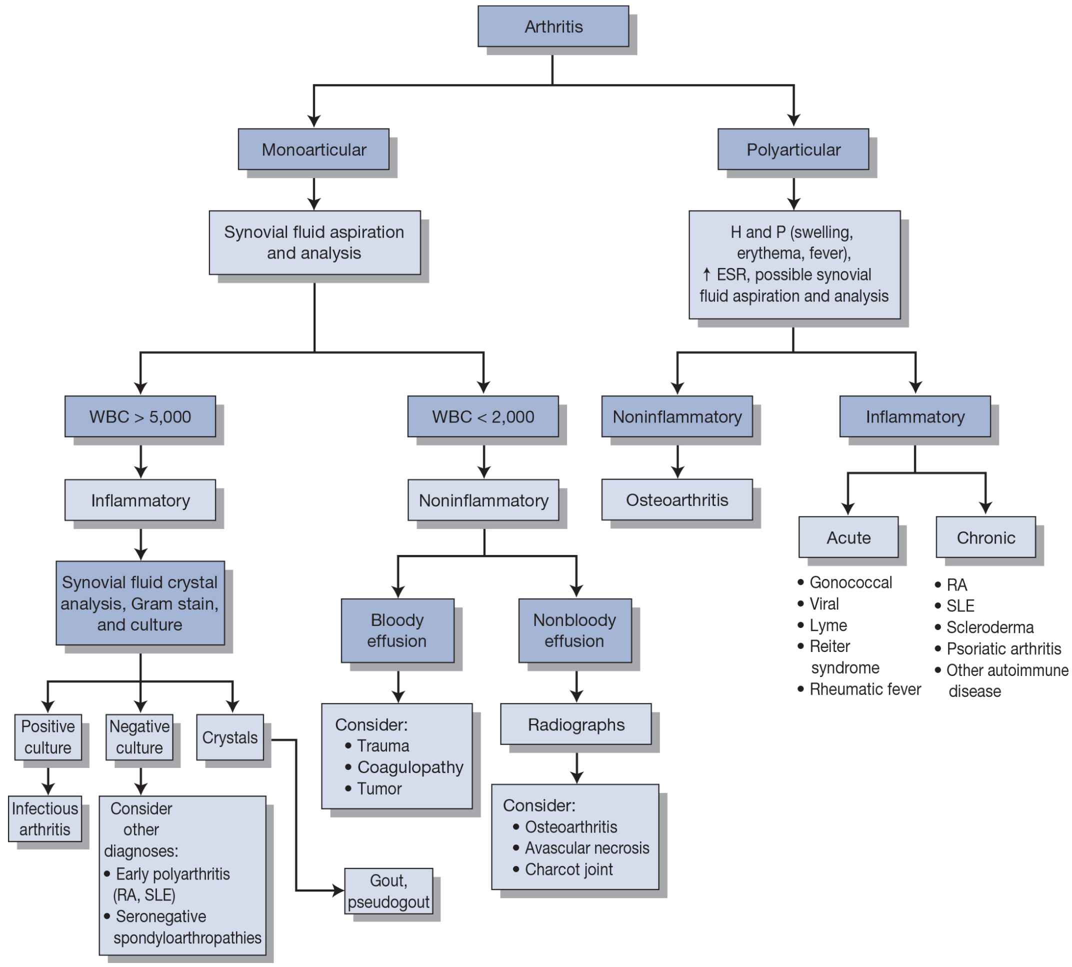


FIGURE 6-7 Evaluation of joint pain.

Myopathies and Pain Syndromes

Idiopathic Inflammatory Myopathies

A. General Characteristics

1. Classification
   a. **Polymyositis** (does not involve skin)
   b. **Dermatomyositis** (associated with characteristic skin rash)

B. Causes

1. Pathologic inflammatory changes in muscle
   a. Disease subtypes include dermatomyositis, polymyositis, inclusion body myositis, antisynthetase syndrome, overlap syndromes, and others.

C. Clinical Features

1. Features common to both polymyositis and dermatomyositis (see Clinical Pearl 6-4)
   a. **Symmetrical proximal muscle weakness** that develops subacutely over weeks or several months
      - The earliest and most severely affected muscle groups are the neck flexors, shoulder girdle, and pelvic girdle muscles
      - Distal extremity weakness is less frequent and typically less severe
   b. Myalgia in 33% of patients
   c. Dysphagia in up to 30% of patients (involvement of striated muscle in the upper GI tract)
   d. More common in female patients
   e. Associated findings include CHF, conduction defects, arthralgias, and interstitial lung disease
2. Features unique to dermatomyositis
   a. *Heliotrope rash* (butterfly)—around eyes, bridge of nose, cheeks
   b. *Gottron papules*—papular, erythematous, scaly lesions over the knuckles (MCP, PIP, DIP)
   c. *V sign*—rash on the face, neck, and anterior chest
   d. *Shawl sign*—rash on shoulders and upper back, elbows, and knees
   e. Periungual erythema with telangiectases
   f. Subcutaneous calcifications in children—can be extremely painful
   g. Associated with vasculitis of the GI tract, kidneys, lungs, and eyes (more common in children)
   h. There is an **increased incidence of malignancy** in older adults (lung, breast, ovary, GI tract, and myeloproliferative disorders). Once dermatomyositis is diagnosed, make an effort to uncover an occult malignancy. Dermatomyositis associated with malignancy often remits once the tumor is removed.

CLINICAL PEARL 6-4

Diagnostic Criteria for Polymyositis

If two of first four → possible polymyositis

If three of first four → probable polymyositis

If all four → definite polymyositis

- Symmetric proximal muscle weakness
- Elevation in serum creatine phosphokinase
- EMG findings of a myopathy
- Biopsy evidence of myositis
- Characteristic rash of dermatomyositis

D. Diagnosis

1. Laboratory
   a. CK level is significantly elevated. CK levels correspond to the **degree of muscle necrosis**, so one can monitor the disease severity
   b. LDH, aldolase, AST, ALT are also elevated
   c. ANA in over 50%
   d. Antisynthetase antibodies **(anti-Jo-1 antibodies)**—abrupt onset of fever, cracked hands, Raynaud phenomenon, interstitial lung disease and fibrosis, arthritis; does not respond well to therapy
   e. Antisignal recognition particle
      - Cardiac manifestations (common)
      - Worst prognosis of all subsets
   f. Anti–Mi-2 antibodies—better prognosis
2. EMG—abnormal in 90% of patients
3. Muscle biopsy
   a. Shows inflammation and muscle fiber fibrosis
   b. Dermatomyositis—**perivascular and perimysial**
   c. Polymyositis and inclusion body myositis—**endomysial**

E. Treatment

1. Corticosteroids are the initial treatment

2. Steroid-sparing immunosuppressive agents (to reduce steroid-induced side effects)—methotrexate, azathioprine
3. Physical therapy

Inclusion Body Myositis

A. General Characteristics

- More common in men (elderly)
- Insidious onset of slowly progressive proximal **and** distal weakness, often leads to delay in diagnosis
- There is early weakness and atrophy of quadriceps, forearm flexors, and tibialis anterior muscles. Involvement is asymmetrical. Facial weakness occurs in one-third of patients, and dysphagia in one-half of patients.
- Patients can also have loss of deep tendon reflexes (nerves are not involved in polymyositis and dermatomyositis)
- Extramuscular manifestations are rare
- Diagnosis—slight elevation of CK levels (relatively low)
- Poor response to therapy
- Not associated with autoantibodies

***Quick* HIT**

Inclusion body myositis is unique for the following reasons: Affects male patients more than female patients, absence of autoantibodies, distal muscle involvement, and relatively low creatine kinase (CK); prognosis is poor.

Polymyalgia Rheumatica

A. General Characteristics

1. Usually occurs in **elderly patients** (rare before the age of 50 years). The mean age of onset is 70 years, and it is more common in women.
2. The cause is unknown, but an autoimmune process may be responsible. There is a possible genetic link (association with HLA-DR4 allele).
3. Self-limited disease (duration of 1 to 2 years).

Quick HIT

About 10% of people with polymyalgia rheumatica develop **temporal arteritis;** up to 40% to 50% of people with temporal arteritis have coexisting polymyalgia rheumatica.

B. Clinical Features

1. Hip and shoulder muscle pain (bilateral)
   a. Often begins abruptly (but may be gradual)
   b. Stiffness in shoulder and hip regions after a period of inactivity is the most prominent symptom
   c. Pain occurs on movement; muscle strength is normal
   d. Profound morning stiffness is common
2. Constitutional symptoms are usually present: Malaise, fever, depression, weight loss, and fatigue
3. Joint swelling
   a. Up to 20% of patients have synovitis in knees, wrists, or hand joints (can be confused with RA)
   b. Synovitis and tenosynovitis around the shoulder may lead to rotator cuff tendonitis or adhesive capsulitis
4. Signs and symptoms of temporal arteritis (if present)

C. Diagnosis

1. Essentially a clinical diagnosis
2. **ESR is usually elevated** and aids in diagnosis
   a. Almost always >50, frequently >100
   b. Correlates with disease activity

D. Treatment: Corticosteroids

1. Start low dose (typically prednisone 15 mg daily). Response usually occurs within 1 to 7 days. Corticosteroids are not curative, but are effective in suppressing inflammation until the disease resolves itself.
2. After 4 to 6 weeks, begin to taper slowly.
3. Most patients (60% to 70%) can stop corticosteroids within 2 years. A few patients have symptoms for up to 10 years.

A 68-year-old man presents with pain in his shoulders, hips, and neck for the last 5 months. The patient reports that the pain is worse in the morning and typically resolves within a few hours. The patient is otherwise healthy and denies headache, visual disturbances, or difficulty chewing. Physical examination does not demonstrate swelling and normal range of motion is noted at all joints. Palpation of the scalp arteries fails to elicit tenderness. Laboratory results reveal the following.

Leukocyte count	8,000/mm^3
Hemoglobin	12.4 g/dL
Platelets	380,000/mm^3
Erythrocyte sedimentation rate	92 mm/hr
TSH	2.1 μU/mL

Which of the following is the best next step in management for this patient’s condition?

A. High-dose corticosteroids
B. Low-dose corticosteroids
C. Temporal artery biopsy
D. Nonsteroidal anti-inflammatory drugs (NSAIDs)

- **The answer is B: Low-dose corticosteroids.** The patient in this question is presenting with signs and symptoms consistent with a diagnosis of polymyalgia rheumatica (PMR), including chronic pain in the shoulders and hips, morning stiffness, elevated ESR, and age greater than 50. Of note, the physical examination in PMR is usually insignificant and the range of motion is typically normal without any associated tenderness or pain. The treatment of choice for PMR is low-dose prednisone. PMR can be associated with temporal arteritis (also known as giant cell arteritis). **(A, C)** Symptoms of temporal arteritis include headache, vision loss, tenderness over the temporal

artery, and jaw claudication. The patient does not have any of these symptoms. **(D)** NSAIDs are helpful in PMR for mild pain or while patients are being tapered off of corticosteroids. However, they are not the first choice in management as they are not as effective as corticosteroids.

Fibromyalgia

A. General Characteristics

1. Adult women account for 80% to 90% of cases.
2. Chronic nonprogressive course with waxing and waning in severity; many patients improve with time.

B. Clinical Features

1. **Stiffness,** body aches (musculoskeletal), fatigue.
   a. Pain is constant and aching, and is aggravated by weather changes, stress, sleep deprivation, and cold temperature. It is worse in the morning.
   b. Rest, warmth, and mild exercise improve the pain.
2. Sleep patterns are disrupted, and sleep is unrefreshing.
3. Anxiety and depression are common.

C. Diagnosis

1. Multiple diagnostic criteria are available (2010 ACR, AAPT, etc.). Key to diagnosis is widespread pain, chronicity of symptoms, and other causes being ruled out.

D. Treatment and Management

1. Initial treatment includes symptomatic treatment using pharmacologic and nonpharmacologic methods (exercise, cognitive behavioral therapy, and education/expectation setting). First-line pharmacologic treatment is a tricyclic antidepressant.
2. Second-line options include SNRIs and neuropathic pain medication (e.g., pregabalin).

Seronegative Spondyloarthropathies

Ankylosing Spondylitis

A. General Characteristics

1. Strong association with **HLA-B27** (90% of patients) (see Table 6-2), however, presence of HLA-B27 should not be considered diagnostic (see Clinical Pearl 6-5).
2. Three times more common in male than in female patients.
3. **Bilateral sacroiliitis** is a prerequisite for making the diagnosis.
4. Onset is in adolescence or young adulthood.
5. It is characterized by “fusion” of the spine in an ascending manner (from lumbar to cervical spine).
6. Course
   a. There is a slow progression, but the course is highly variable; acute exacerbations are common.
   b. Life expectancy is usually normal.
   c. The first 10 years of the disease can give an indication of long-term severity.

CLINICAL PEARL 6-5

Seronegative Spondyloarthropathies

Diseases that belong to seronegative spondyloarthropathies include the following:

- Ankylosing spondylitis
- Reactive arthritis (and Reiter syndrome)
- Psoriatic arthritis
- Arthropathy of IBD
- Undifferentiated spondyloarthropathies

Seronegative spondyloarthropathies have the following **in common:**

- Negative RF
- Strong association with HLA-B27 antigen
- Oligoarthritis (asymmetrical)
- Enthesitis (inflammation at sites of insertion of fascia, ligament, or tendon to bone)
- Inflammatory arthritis (axial and sacroiliac joints)
- Extra-articular features (eyes, skin, genitourinary tract)
- Familial predisposition

***Quick* HIT**

In ankylosing spondylitis, low back pain and stiffness are characteristically worse in the morning and better as the day progresses. They **improve with activity** and a hot shower and worsen with rest or inactivity.

B. Clinical Features

1. Low back pain and stiffness (secondary to sacroiliitis)—limited motion in lumbar spine
2. Neck pain and limited motion in cervical spine—occurs later in course of disease
3. **Enthesitis**—inflammation at tendinous insertions into bone (Achilles tendon and supraspinatus tendon)
4. With extensive spinal involvement, the spine becomes brittle and is prone to fractures with minimal trauma. Severe spinal cord injury can occur with such trauma
5. Chest pain and diminished chest expansion—due to thoracic spine involvement

6. Shoulder and hip pain—most commonly the peripheral joints are affected
7. Constitutional symptoms—fatigue, low-grade fever, weight loss
8. Extra-articular manifestations
   a. Eye involvement (most common)—acute **anterior uveitis** or iridocyclitis
   b. Other extra-articular features are rare, but may involve the following systems: Cardiac **(AV heart block and aortic insufficiency),** renal, pulmonary, and nervous systems
9. Loss of lumbar lordosis can occur as disease advances, leading to inability to stand upright. When severe and symptomatic, this may require spine reconstruction

***Quick* HIT**

Complications of Ankylosing Spondylitis

- Restrictive lung disease
- Cauda equina syndrome
- Spine fracture with spinal cord injury
- Osteoporosis
- Spondylodiscitis

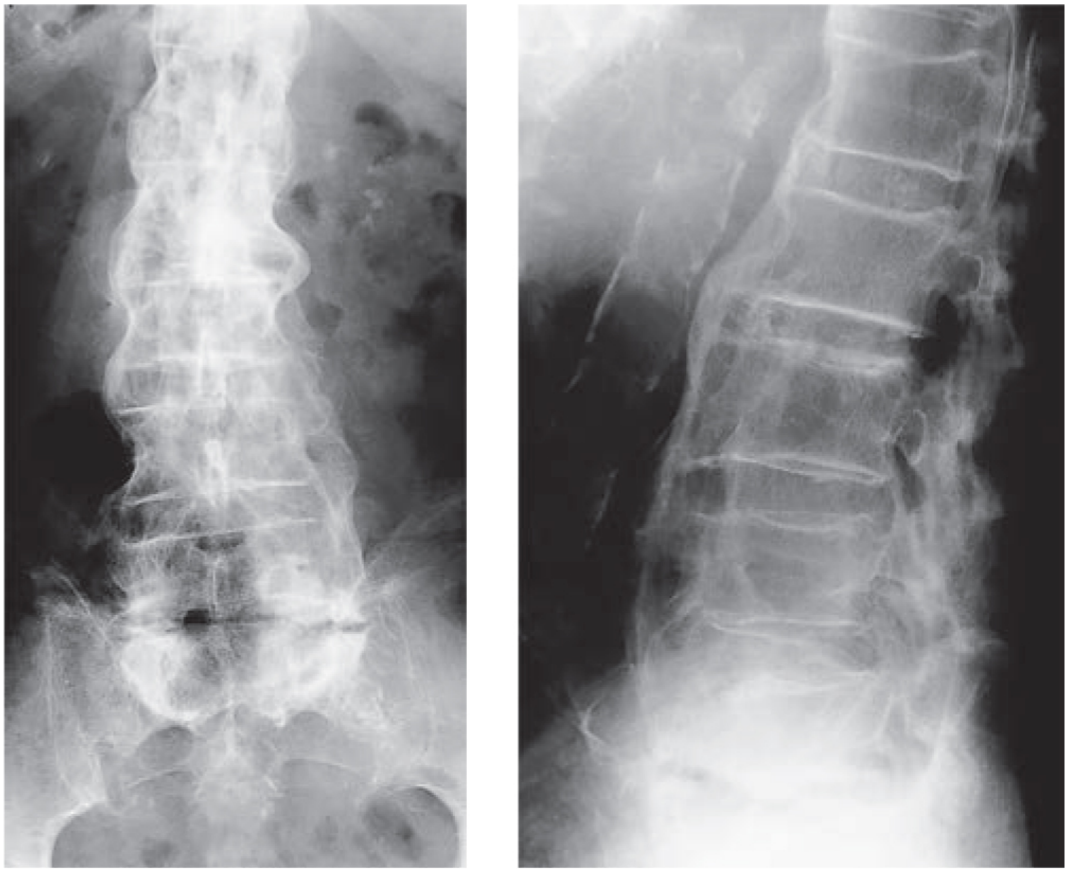
C. Diagnosis

1. Imaging studies of lumbar spine and pelvis (plain film, MRI, or CT) reveal sacroiliitis—sclerotic changes in the sacroiliac area. Eventually, the vertebral columns fuse, producing **"bamboo spine"** (Figure 6-8)
2. Elevated ESR in up to 75% of patients (due to inflammation)—nonspecific
3. HLA-B27 is not necessary for diagnosis. Present in 8% of general population

D. Treatment

1. NSAIDs (indomethacin) for symptomatic relief
2. If insufficient response, anti-TNF medications (etanercept, infliximab). For those with a contraindication to anti-TNF medications, an anti–IL-17 monoclonal antibody (e.g., secukinumab, ixekizumab) can be used

3. Physical therapy (maintaining good posture, extension exercises)
4. Surgery may be necessary in some patients with severe spinal deformity
5. Patients with ankylosing spondylitis who sustain even minor trauma and who complain of neck or back pain should be strictly immobilized to prevent spinal cord injury until thorough imaging studies (including CT scan and possibly MRI) are obtained



A B

FIGURE 6-8 **Anteroposterior (A) and lateral (B) radiographs of the lumbar spine in a patient with ankylosing spondylitis. This patient presented to the emergency department with increasing back pain after a motor vehicle collision. Careful review of the radiographs shows a cleft in the fusion mass at L5–S1. A bone scan confirmed increased activity at this level, which is indicative of a new fracture.**
(Reprinted with permission from Konopka J, Fogel HA, Diwan A. Inflammatory arthritides. In: Truumees E, Prather H, eds. *Orthopaedic Knowledge Update® Spine 6: Print + Ebook*. Wolters Kluwer; 2021:513.)

A 27-year-old man presents with 6 months of worsening low back pain. The pain is worse in the morning and associated with morning "stiffness" that improves with walking and exercise. The patient feels well and denies any systemic symptoms. Physical examination reveals limited range of motion on forward flexion of her lower back. X-ray reveals the presence of a "bamboo spine."

Which of the following is the most common extra-articular manifestation of this patient's condition?

A. Aortic valve insufficiency
B. Lung fibrosis
C. Anterior uveitis
D. Oral ulcers

- **The answer is C: Anterior uveitis.** The patient in this question is presenting with signs, symptoms, and radiologic findings consistent with a diagnosis of ankylosing spondylitis (AS). The most common extra-articular manifestation of AS is anterior uveitis: inflammation in the anterior chamber of the eye. This can cause erythema, pain, and photophobia. **(A, B)** Both aortic valve insufficiency and lung fibrosis are less commonly associated with AS. **(D)** Oral ulcers are associated with systemic lupus erythematosus (SLE) and Crohn disease, but are not associated with AS.

Reactive Arthritis

A. General Characteristics

1. Reactive arthritis is asymmetric inflammatory oligoarthritis of lower extremities (upper extremities less common) (see Table 6-7). The arthritis is preceded by an infectious process that is remote from the site of arthritis (1 to 4 weeks prior), usually after enteric or urogenital infections.

2. The triad of postinfectious arthritis, conjunctivitis, and urethritis was previously known as Reiter syndrome.
3. It occurs mostly in HLA-B27–positive individuals.
4. The organisms usually associated with reactive arthritis include those that cause GI or GU infections: *Salmonella, Shigella, Campylobacter, Chlamydia, Yersinia.*

Quick HIT

Reactive arthritis is a clinical diagnosis. If any patient has acute asymmetric arthritis that progresses sequentially from one joint to another, reactive arthritis should be in the differential diagnosis.

TABLE 6-7 Causes of Joint Pain

Polyarticular Joint Pain	Monoarticular Joint Pain
RA	Osteoarthritis
SLE	Gout
Viral arthritis	Pseudogout
Reiter syndrome	Trauma
Rheumatic fever	Septic arthritis
Lyme disease	Hemarthrosis
Gonococcal arthritis	
Drug-induced arthritis	

Quick HIT

The term **undifferentiated spondyloarthropathy** is used when a patient has features of reactive arthritis but there is no evidence of previous infection (in the GI or genitourinary tract) and the classic findings are absent.

B. Clinical Features

1. Look for evidence of infection (GI or genitourinary) 1 to 4 weeks before the onset of symptoms.
2. Asymmetric arthritis—new joints may be involved sequentially over days. Joints are painful, with effusions and lack of mobility.
3. Fatigue, malaise, weight loss, and fever are common.
4. Joint pain may persist or recur over a long-term period.

C. Diagnosis

Send synovial fluid for analysis (to rule out infection or crystals). There is no test specific to reactive arthritis.

D. Treatment

1. Treat the underlying infection (does not necessarily treat the arthritis).
2. NSAIDs are first-line therapy.
3. If there is no response, then steroids can be used.
4. For chronic disease, treatment with a DMARD (e.g., sulfasalazine, methotrexate) should be used.

Psoriatic Arthritis

- Develops in 10% to 30% of patients with psoriasis.
- It is typically gradual in onset. Patients usually have skin disease for months to years before arthritis develops.
- Usually asymmetric and polyarticular. Characteristic dactylitis (**"sausage digits"**) and **nail pitting** may also be present.
- Upper extremities most often involved; smaller joints more common than large joints.
- Initial treatment is NSAIDs, but persistent arthritis may require methotrexate or anti-TNF agents. Steroids are typically not used.

Vasculitis

Vasculitis Overview (Figure 6-9)

1. Vasculitis refers to inflammation within blood vessel walls
2. Vasculitides are classified based on the size of the vessels involved:
   a. Large vessel: aorta and major branches
   b. Medium vessel: medium arteries
   c. Small vessel: small arteries and capillaries. Further subdivided into ANCA-associated vasculitides and immune complex vasculitides
   d. Variable vessel

Large-Vessel Vasculitides

Temporal/Giant Cell Arteritis

A. General Characteristics

1. Vasculitis of unknown cause; typical patient is >50 years of age; twice as common in women as men (see Clinical Pearl 6-6).
2. The temporal arteries are most frequently affected, but it may involve other arteries, such as the aorta or carotids. Carotid bruits, decreased pulses in the arms, and aortic regurgitation may also be observed.
3. Associated with increased risk of aortic aneurysm and aortic dissection.

B. Clinical Features

1. Constitutional symptoms of malaise, fatigue, weight loss, and low-grade fever
2. Headaches—may be severe
3. Visual impairment (in only 25% to 50%)
   a. Caused by involvement of ophthalmic artery
   b. Optic neuritis; amaurosis fugax; may lead to **blindness** in up to 50% if not treated early and aggressively
4. Jaw pain with chewing—intermittent **claudication of jaw/tongue** when chewing

5. Tenderness over temporal artery; absent temporal pulse
6. Palpable nodules
7. **Forty percent of patients also have polymyalgia rheumatica**

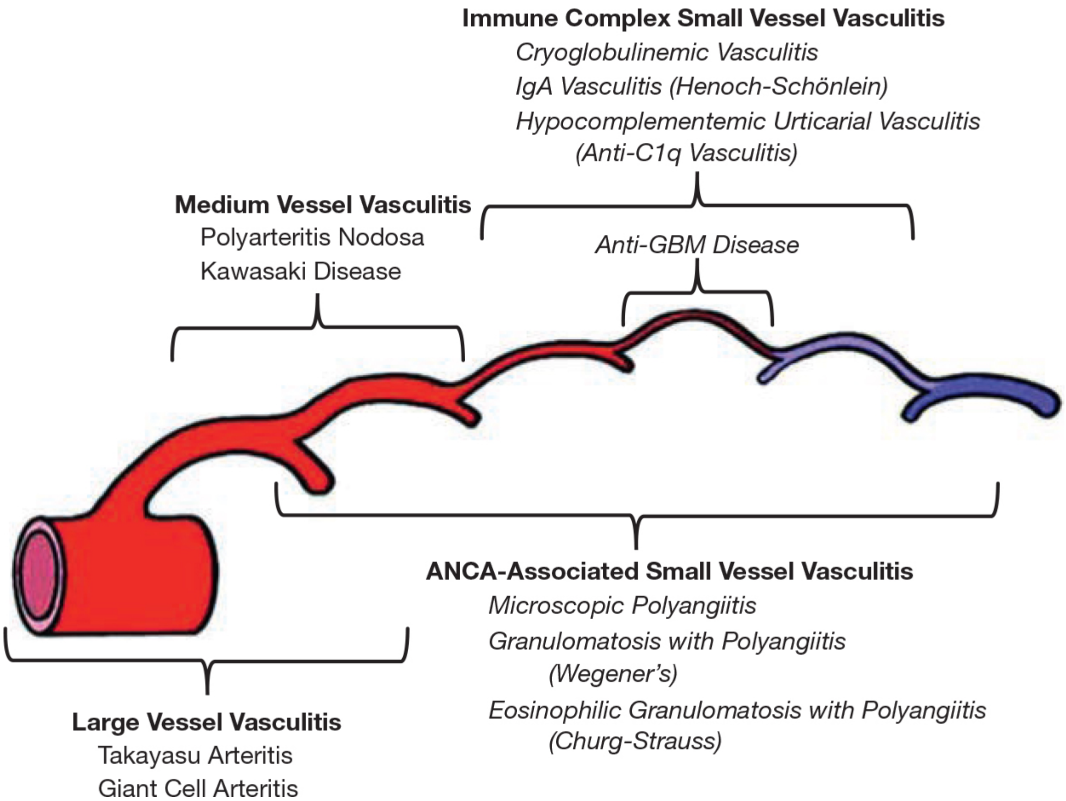


FIGURE 6-9 Diagram depicting the usual distribution of vessel involvement by large vessel vasculitis, medium vessel vasculitis, and small vessel vasculitis. All three major categories of vasculitis can affect any size artery, although large vessel vasculitis most often affects large arteries. Medium vessel vasculitis predominantly affects medium arteries, but small arteries may be affected. Small vessel vasculitis predominantly affects venules and capillaries. Immune complex small vessel vasculitis rarely affects arteries. Note that ANCA (antineutrophil cytoplasmic antibody)-associated vasculitis affects a broader spectrum of vessels than does immune complex vasculitis.
(Reprinted with permission from Frontera WR, DeLisa JA, Gans BM, et al. *DeLisa's Physical Medicine and Rehabilitation: Principles and Practice*. 6th ed. Wolters Kluwer; 2019. Figure 32-2.)

C. Diagnosis

1. **ESR elevated** (but normal ESR does not exclude the diagnosis)

2. Biopsy of the temporal artery has a sensitivity of 90%. A single negative biopsy does not exclude the diagnosis

***Quick* HIT**

Keys to Diagnosing Temporal Arteritis

- Age >50 years
- New headache
- Tender/palpable temporal artery
- High ESR
- Jaw claudication

D. Treatment

1. Use high-dose steroids (prednisone) early to prevent blindness.
   a. Start treatment **immediately**, even if temporal arteritis is only suspected. **Do not wait for biopsy results**. If visual loss is present, admit the patient to the hospital for IV steroids; otherwise, start oral prednisone.
   b. If the diagnosis is confirmed, continue treatment for at least 4 weeks, then taper gradually, but maintain steroid therapy for up to 2 to 3 years. Relapse is likely to occur if steroids are stopped prematurely.

CLINICAL PEARL 6-6

Vasculitis

- In all of the vasculitic syndromes, blood vessels are inflamed and vascular necrosis can result. Findings depend on the size of the vessel involved and the location of involvement (target organ ischemia).
- If any patient has a systemic illness that has not been explained by another process (or has ischemia involving one or more systems), entertain the diagnosis of vasculitis.
- Classified according to size of vessel
  - **Large vessel:** Takayasu arteritis, temporal arteritis
  - **Medium vessel:** PAN, Kawasaki disease (pediatric)
  - **Small vessel:**
    - ANCA-associated: GPA, EGPA, microscopic polyangiitis
    - Immune complex: cryoglobulinemic, IgA vasculitis (pediatric)
  - Variable vessel: Behçet syndrome

2. Follow up on ESR levels to monitor effectiveness of treatment.
3. Visual loss in one eye may be temporary or permanent. Prompt and aggressive steroid treatment is primarily given to prevent involvement of the other eye, but it may improve the visual outcome in the affected eye as well.
4. Even if untreated, the disease is usually eventually self-limiting in most patients, although vision loss may be permanent.

Quick HIT

If temporal arteritis is suspected, begin steroids and order a temporal artery biopsy.

Quick HIT

Suspect Takayasu arteritis in a young woman with:
- Decreased/absent peripheral pulses
- Discrepancies of BP (arm vs. leg)
- Arterial bruits

Takayasu Arteritis

A. General Characteristics

1. Most common in young Asian women
2. Granulomatous vasculitis of aortic arch and its major branches—leading to fibrosis and potentially causing to stenosis or narrowing of vessels
3. Diagnosed via arteriogram

B. Clinical Features

1. Constitutional symptoms—fever, night sweats, malaise, arthralgias, fatigue
2. Pain and tenderness over involved vessels
3. Absent pulses in carotid, radial, or ulnar arteries; aortic regurgitation may be present
4. Signs and symptoms of ischemia eventually develop in areas supplied by involved vessels
5. Severe complications include limb ischemia, aortic aneurysms, aortic regurgitation, stroke, and secondary HTN due to renal artery stenosis. The main prognostic predictor is the presence or absence of these complications
6. Causes visual disturbances due to ocular involvement and hemorrhage of retinal arteries

C. Treatment

1. Steroids such as prednisone may relieve the symptoms.
2. Treat HTN.
3. Surgery or angioplasty may be required to recannulate stenosed vessels. Bypass grafting is sometimes necessary.

Medium-Vessel Vasculitides

Polyarteritis Nodosa

A. General Characteristics

1. Vasculitis of medium-sized vessels involving the nervous system and GI tract.
2. Can be associated with **hepatitis B**, HIV, and drug reactions.
3. Pathophysiology: PMN invasion of all layers and fibrinoid necrosis plus resulting intimal proliferation lead to reduced luminal area, which results in ischemia, infarction, and aneurysms.
4. Necrosis is segmented, leading to “rosary sign” as a result of aneurysms.

Quick HIT

There is **no pulmonary involvement** in PAN (which distinguishes it from GPA).

B. Clinical Findings

1. Early symptoms are fever, weakness, weight loss, myalgias, arthralgias, and abdominal pain (bowel angina).
2. Other findings are HTN, mononeuritis multiplex, and livedo reticularis.

C. Diagnosis

1. Diagnosis is made by biopsy of involved tissue or mesenteric angiography.
2. ESR is usually elevated, and p-ANCA may be present.
3. Test for fecal occult blood.

D. Prognosis and Treatment

The prognosis is poor, but is improved to a limited extent with treatment. Start with corticosteroids. If severe, add azathioprine or methotrexate. Cyclophosphamide is used for severe cases.

ANCA-Associated Small-Vessel Vasculitides

Granulomatosis With Polyangiitis (GPA)

A. General Characteristics

Vasculitis predominantly involving the kidneys and upper and lower respiratory tract (sometimes other organs as well)

B. Clinical Features

1. Upper respiratory symptoms (e.g., **sinusitis**); purulent or bloody nasal discharge
2. Oral ulcers (may be painful)
3. Pulmonary symptoms (cough, hemoptysis, dyspnea)
4. Renal involvement (glomerulonephritis—may have rapidly progressive renal failure)
5. Eye disease (conjunctivitis, scleritis)
6. Musculoskeletal (arthralgias, myalgias)
7. Tracheal stenosis
8. Constitutional findings (e.g., fever, weight loss)

***Quick* HIT**

Most patients with GPA also have sinus disease, pulmonary disease, and glomerulonephritis. Complications of immunosuppression, renal/pulmonary disease, and CV disease account for the majority of deaths.

C. Diagnosis

1. Chest radiograph is abnormal (nodules or infiltrates).
2. Laboratory findings: Markedly elevated ESR, anemia (normochromic normocytic), hematuria, **positive c-ANCA in 90%** of patients—sensitive and specific; thrombocytopenia may be present.
3. Tissue biopsy of an affected organ (e.g., lung, kidney) is often important in making the diagnosis.

D. Prognosis and Treatment

1. Prognosis is poor if untreated (90% mortality within 2 years).
2. Treatment is based on severity of disease. If mild, then steroids with methotrexate are typically used. If severe and organ- or life-threatening, then steroids with rituximab or cyclophosphamide are typically used. Other immunosuppressive agents can be used for chronic maintenance therapy.

Eosinophilic Granulomatosis With Polyangiitis (EGPA)

- Vasculitis involving many organ systems (respiratory, cardiac, GI, skin, renal, neurologic)
- Clinical features include constitutional findings (fever, fatigue, weight loss), prominent respiratory tract findings (**asthma,** dyspnea), skin lesions (subcutaneous nodules, palpable purpura), as well as **eosinophilia.**
- Diagnosis is made by biopsy of lung or skin tissue (prominence of eosinophils). **It is associated with p-ANCA.**
- The prognosis was historically poor, but has improved dramatically with early steroids and other immunosuppressive agents.

Microscopic Polyangiitis

- Like GPA, commonly involves the skin (palpable purpura), lungs (cough, dyspnea, hemoptysis, pulmonary fibrosis, pulmonary hypertension), and kidneys (glomerulonephritis)
- Unlike GPA, does not typically have nasopharyngeal involvement
- Can also be distinguished from GPA by biopsy, which shows necrotizing vasculitis without granulomas

Immune Complex Small-Vessel Vasculitides

Cryoglobulinemic Vasculitis

- Caused by deposition of cryoglobulins, which are immunoglobulins that precipitate in cold temperatures.
- Classified into Type I, Type II, and Type III based on the type and clonality of immunoglobulins.

- Most common cause is chronic HCV infection. Other causes include chronic HBV infection, HIV infection, and other causes of chronic liver disease (e.g., autoimmune hepatitis, primary biliary cirrhosis).
- Proposed mechanism is deposition of antigen–antibody complexes (such as HCV antibodies) in small vessels, which leads to complement activation and inflammation. Liver disease may contribute to decreased immune complex clearance, which leads to greater tissue deposition and disease activity.
- Common clinical manifestations include palpable purpura, renal disease, arthralgias/arthritis, peripheral neuropathy, and hypocomplementemia. Pulmonary and CNS involvement are rare.
- Diagnosis is made clinically, by the presence of circulating cryoglobulins, and by a biopsy showing leukocytoclastic vasculitis (inflammation with polymorphonuclear leukocyte nuclear debris). Patients should be tested for underlying HCV, HBV, and HIV.

Variable-Vessel Vasculitis

Behçet Syndrome

- An autoimmune, multisystem vasculitic disease; cause is unknown.
- Clinical features: painful, sterile oral and genital ulcerations (**pathergy**), arthritis (knees and ankles most common), **eye involvement** (uveitis, optic neuritis, iritis, conjunctivitis), CNS involvement (meningoencephalitis, intracranial HTN), fever, and weight loss.
- Diagnosis is made using clinical criteria, tissue biopsy can be helpful.
- Treatment is with colchicine for most patients, with steroids for more severe or recurrent disease.

Diseases of the Renal and Genitourinary System

7

Mark D. Duncan

Renal Failure

Acute Kidney Injury (AKI)

A. General Characteristics

1. Definition:
   a. KDIGO definition most commonly used. Any of the following meet criteria for AKI:
   - Increase in serum creatinine by at least 0.3 mg/dL or more, within 48 hours
   - Increase in serum creatinine by at least 1.5x the baseline value, within the prior 7 days
   - Urine output of less than 0.5 mL/kg/hr for at least 6 hours

   b. RIFLE criteria are another set of definitions for renal injury:
   - **RISK:** 1.5-fold increase in the serum creatinine or GFR decrease by 25% or urine output <0.5 mL/kg/hr for 6 hours.
   - **INJURY:** Twofold increase in the serum creatinine or GFR decrease by 50% or urine output <0.5 mL/kg/hr for 12 hours.
   - **FAILURE:** Threefold increase in the serum creatinine or GFR decrease by 75% or urine output of <0.5 mL/kg/hr for 24 hours, or anuria for 12 hours.
   - **LOSS:** Complete loss of kidney function (i.e., requiring dialysis) for more than 4 weeks.
   - **ESRD:** Complete loss of kidney function (i.e., requiring dialysis) for more than 3 months.

Quick HIT

Types of AKI (see Figure 7-1)

- **Prerenal AKI**—decrease in renal blood flow (60% to 70% of cases)
- **Intrinsic AKI**—damage to renal parenchyma (25% to 40% of cases)
- **Postrenal AKI**—urinary tract obstruction (5% to 10% of cases)

2. AKI may be nonoliguric, oliguric, or anuric. Severe AKI may occur without a reduction in urine output (nonoliguric AKI).
   a. General goals of therapy are reversing the initial insult to the kidney and/or supportive care as GFR recovers, as well as preventing fulminant kidney failure requiring temporary or permanent hemodialysis.
3. Weight gain and edema are most common findings in patients with AKI. This is due to a positive water and sodium ($Na+$) balance.
4. Characterized by **azotemia** (elevated BUN and Cr).
   a. Elevated BUN is also seen with catabolic drugs (e.g., steroids), GI/soft tissue bleeding (due to RBC digestion and reabsorption of urea), and dietary protein intake.
   b. Elevated Cr is also seen with increased muscle breakdown and various drugs. The baseline Cr level varies proportionately with muscle mass.
5. Prognosis
   a. More than 80% of patients in whom AKI develops recover completely. However, prognosis varies widely depending on the severity of renal failure and other comorbidities.
   b. The older the patient and the more severe the insult, the lower is the likelihood of complete recovery.
   c. The most common cause of death is infection (75% of all deaths), followed by cardiorespiratory complications. Other nonfatal complications include chronic kidney injury and need for dialysis.

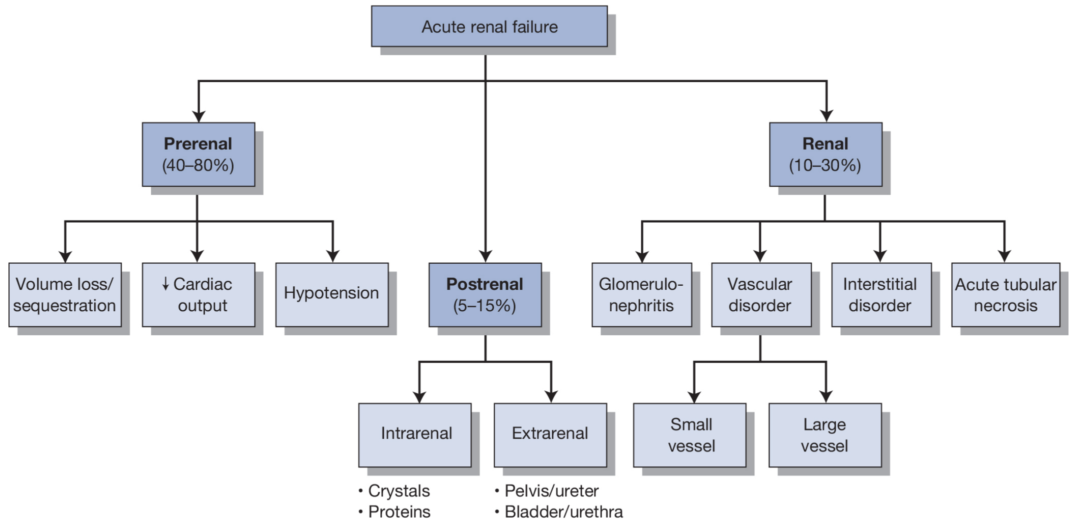


FIGURE 7-1 **Causes of AKI.**

***Quick* HIT**

Monitoring a Patient With AKI

- Daily weights, intake, and output (worsening volume status can be an indication for urgent dialysis)
- BP
- Serum electrolytes (hyperkalemia and acidosis can also be indications for urgent dialysis, also tend toward hyponatremia and hyperphosphatemia)
- Hb and Hct (for anemia)
- Watch for signs of infection

B. Categories (Figure 7-1)

1. Prerenal failure (see also Clinical Pearl 7-1)
   a. Most common cause of AKI; potentially reversible
   b. Etiology (decrease in systemic arterial blood volume or renal perfusion leading to renal ischemia)—can complicate any disease that causes hypovolemia, low cardiac output, or systemic vasodilation
      - Hypovolemia—dehydration, excessive diuretic use, poor fluid intake, vomiting, diarrhea, burns, hemorrhage
      - CHF, cardiorenal syndrome
      - Hypotension (systolic BP below 90 mm Hg), from sepsis, excessive antihypertensive medications, bleeding, dehydration

- Renal arterial obstruction (kidney is hypoperfused despite elevated blood pressure)
- Cirrhosis, hepatorenal syndrome
- In patients with decreased renal perfusion, NSAIDs (constrict afferent arteriole), ACE inhibitors (cause efferent arteriole vasodilation), and cyclosporin can precipitate prerenal failure

c. Pathophysiology

- Renal blood flow decreases enough to lower the GFR, which leads to decreased clearance of metabolites (BUN, Cr, uremic toxins).
- Because the renal parenchyma is undamaged, tubular function (and therefore the concentrating ability) is preserved. Therefore, the kidney responds appropriately, conserving as much sodium and water as possible.
- This form of AKI is reversible on restoration of blood flow; but if hypoperfusion persists, ischemia results and can lead to acute tubular necrosis (ATN) (see below).

d. Clinical features—signs of volume depletion (dry mucous membranes, hypotension, tachycardia, decreased tissue turgor, oliguria/anuria)

e. Laboratory findings

- **Oliguria**—**always** found in prerenal failure (this is to preserve volume)
- Increased BUN-to-serum Cr ratio (>**20:1** is the classic ratio)—because kidney can reabsorb urea to increase sodium and water retention
- Increased urine osmolality (>500 mOsm/kg H_2O)—because the kidney is able to appropriately reabsorb water
- Decreased urine Na+ (<20 mEq/L with fractional excretion of sodium [FENa] <1%) because Na+ is avidly reabsorbed
- Increased urine-plasma Cr ratio (>40:1)—because much of the filtrate is reabsorbed (but not the creatinine)
- Bland urine sediment, indicating lack of significant cellular damage to glomeri or tubules

CLINICAL PEARL 7-1

Diagnostic Approach in AKI

- History and physical examination.
- The first thing to do is to determine the duration of renal failure. A baseline Cr level provides this information.
- The second task is to determine whether AKI is due to prerenal, intrarenal, or postrenal causes. This is done via a combination of H&P and laboratory findings.
    - Signs of volume depletion and CHF or cirrhosis suggest a prerenal etiology.
    - Signs of an allergic reaction (rash) suggest acute interstitial nephritis (an intrinsic renal etiology).
    - A suprapubic mass, BPH, or bladder dysfunction suggests a postrenal etiology.
- Medication review
- Urinalysis
- Urine chemistry (FENa or FEUrea, osmolality, urine Na+, urine Cr, urine BUN)
- Renal ultrasound (to rule out obstruction)

TABLE 7-1 Studies to Differentiate Prerenal From Intrinsic AKI

	Prerenal	Intrinsic Renal
Urinalysis	Hyaline casts	Abnormal
BUN/Cr Ratio	>20:1	<20:1
FENa	<1%	>2–3%
Urine Osmolality	>500 mOsm	250–300 mOsm
Urine Sodium	<20	>40

Quick HIT

Prerenal Failure Versus ATN

	Prerenal Failure	**ATN**
Urine osmolarity	High	Similar to plasma
Urine Na^+	<20	>40
FENa	<1%	>1%
Urine sediment	Scant	Full brownish pigment, granular casts with epithelial casts

2. Intrinsic renal failure (see Table 7-1 and Clinical Pearl 7-2)
   a. Kidney tissue (interstitium, glomeruli, tubules) is damaged such that glomerular filtration and tubular function are significantly impaired. Thus, kidneys are unable to concentrate urine effectively.
   b. Causes
      - Tubular disease (ATN)—can be caused by ischemia (most common cause), nephrotoxins (see Clinical Pearls 7-3 and 7-4).
      - Glomerular disease (acute glomerulonephritis [GN])—for example, Goodpasture syndrome, granulomatosis with polyangiitis, poststreptococcal GN, lupus
      - Vascular disease—for example, renal artery occlusion, TTP, HUS
      - Interstitial disease—for example, allergic interstitial nephritis, often due to a hypersensitivity reaction to medication (see Tubulointerstitial Diseases section)
   c. Clinical features depend on the cause. Edema is usually present. Recovery may be possible but takes longer than in prerenal failure
   d. Laboratory findings
      - Decreased BUN-to-serum Cr ratio (<20:1, typically closer to 10:1 ratio) in comparison with prerenal failure. Both BUN and Cr levels are still elevated, but less urea is reabsorbed than in prerenal failure as kidney is no longer actively reabsorbing it.
      - Increased urine Na+ (>40 mEq/L with FENa > 2% to 3%)—because Na+ is poorly reabsorbed

- Decreased urine osmolality (<350 mOsm/kg H_2O)—because renal water reabsorption is impaired
- Decreased urine–plasma Cr ratio (<20:1)—because filtrate cannot be reabsorbed

Quick HIT

Note that prerenal azotemia and ischemic AKI are part of a spectrum of manifestations of renal hypoperfusion. The latter differs in that injury to renal tubular cells occurs.

CLINICAL PEARL 7-2

Rhabdomyolysis

1. Skeletal muscle breakdown caused by trauma, crush injuries, prolonged immobility, seizures, snake bites.
2. Release of muscle fiber contents (myoglobin) into bloodstream. Myoglobin is toxic to kidneys, which can lead to AKI via tubular damage and obstruction.
3. Presents with sequelae of cell death: markedly elevated creatine phosphokinase (CPK), hyperkalemia, hypocalcemia (due to released phosphate), hyperuricemia.
4. Treat with IV fluids, mannitol (osmotic diuretic) and bicarbonate (drives K back into cells).

CLINICAL PEARL 7-3

Causes of Acute Tubular Necrosis (ATN)

- Ischemic AKI
- Secondary to severe decline in renal blood flow, as in shock, hemorrhage, sepsis, disseminated intravascular coagulation, heart failure.
- Ischemia results in the death of tubular cells.
- Nephrotoxic AKI
- Injury secondary to substances that directly injure renal parenchyma and result in cell death.
- Causes include antibiotics (aminoglycosides, vancomycin), radiocontrast agents, NSAIDs (especially in the setting of CHF), poisons, myoglobinuria (from muscle damage, rhabdomyolysis, strenuous exercise), hemoglobinuria (from hemolysis), chemotherapeutic drugs (cisplatin), and kappa and gamma light chains produced in multiple myeloma.

Quick HIT

Tests for Postrenal Failure

- Ultrasound—look for obstruction, hydronephrosis
- Catheter—look for large volume of urine

3. Postrenal failure
   a. Least common cause of AKI
   b. Obstruction of any segment of the urinary tract (with intact kidney) causes increased tubular pressure (urine produced cannot be excreted), which leads to decreased GFR. Blood supply and renal parenchyma are intact. Note that both kidneys must be obstructed (e.g., prostatic enlargement) for creatinine to rise
   c. Renal function is restored if obstruction is relieved before the kidneys are damaged.
   d. Postrenal obstruction, if untreated, can lead to ATN
   e. Causes
      - Urethral obstruction secondary to enlarged prostate (BPH) is the most common cause
      - Obstruction of solitary kidney

- Nephrolithiasis
- Obstructing neoplasm (bladder, cervix, prostate, and so on)
- Retroperitoneal fibrosis
- Ureteral obstruction is an uncommon cause because obstruction must be bilateral to cause renal failure

CLINICAL PEARL 7-4

Course of ATN

- Onset (insult)
- **Oliguric phase**
  - Azotemia and uremia—average length 10 to 14 days
  - Urine output
- **Diuretic phase**
  - Begins when urine output is >500 mL/day
  - High urine output due to the following: fluid overload (excretion of retained salt, water, other solutes that were retained during oliguric phase); osmotic diuresis due to retained solutes during oliguric phase; tubular cell damage (delayed recovery of epithelial cell function relative to GFR)
- **Recovery phase**—recovery of tubular function

CLINICAL PEARL 7-5

Urine Osmolality

1. Urine osmolality is a measure of urine concentration. The higher the osmolality, the more concentrated the urine.
2. Dehydration in a healthy person leads to increase in urine concentration (osmolality) as follows: Dehydration causes low intravascular volume, which triggers ADH release, which stimulates reabsorption of water from kidney to fill the vasculature. Increased water reabsorption leads to more concentrated urine.
3. In ATN, the tubule cells are damaged and cannot reabsorb water (or sodium); so the urine cannot be concentrated, which leads to low urine osmolality.

Quick HIT

Diagnosis of AKI is usually made by finding elevated BUN and Cr levels. The patient is usually asymptomatic.

Quick HIT

Consider the Following Workup for AKI If the Cause Is Not Obvious

- Urinalysis
- Urine chemistry
- Serum electrolytes (Na+, K+, BUN, Cr), CBC
- Bladder catheterization to rule out obstruction (diagnostic and therapeutic)
- Renal ultrasound to look for obstruction

C. Diagnosis

1. Blood tests (see also Clinical Pearl 7-5)
   a. Elevation in BUN and Cr levels. Be aware that small changes in Cr may reflect a much more significant decrease in GFR
   b. Electrolytes (retention of K+, PO_4^{3-}, drop in HCO_3^- indicating acidosis, decrease in Na+ due to fluid retention)
   c. Albumin levels to monitor for nephrotic syndrome
   d. CBC with differential
2. Urinalysis (Figure 7-2 and Table 7-2)
   a. A dipstick test positive for protein (3+, 4+) suggests proteinuria, but should be followed up with a spot protein to creatinine ratio or a 24-hour urine collection for proteinuria (to assess for nephrotic syndrome)
   b. Microscopic examination of the urine sediment:
      - **Crystals** indicate presence of stones.
      - **Micro-organisms** are seen in both infection and nonpathogenic colonization (differentiation made based on symptoms).
      - **Granular casts** degeneration of cells and protein aggregates seen in ATN ("muddy brown" casts)
      - **Hyaline casts** are devoid of contents (seen in prerenal failure).
      - **RBC casts** indicate glomerular disease.

- **WBC casts** indicate renal parenchymal inflammation.
- **Fatty casts** indicate nephrotic syndrome.

3. Urine chemistry—to distinguish between different forms of AKI
   a. Urine Na^+, Cr, and osmolality: Urine Na^+ **depends on dietary intake.**
   b. FENa: collect urine and plasma electrolytes simultaneously = $[(U_{Na})/(P_{Na})/(U_{Cr})/(P_{Cr}) \times 100]$, where U = urine and P = plasma.
   - Values below 1% suggest prerenal failure.
   - Values above 2% to 3% suggest ATN.
   - **FENa is most useful if oliguria is present.**
   - If patient is on diuretics, U_{Na} will be artificially elevated and fractional excretion of urea (FEUrea) must be used instead.
4. Urine culture and sensitivities—if infection is suspected
5. Renal ultrasound
   a. Primarily useful for evaluating kidney size and **for excluding urinary tract obstruction (i.e., postrenal failure)**—presence of bilateral hydronephrosis or hydroureter
6. Renal biopsy—useful in unknown causes, especially if intrinsic renal failure is suspected

Quick HIT

In evaluating a patient with AKI, first exclude prerenal and postrenal causes, and then, if necessary, investigate intrinsic renal causes.

D. Complications

1. ECF volume expansion and resulting pulmonary edema—treat with a diuretic (furosemide)

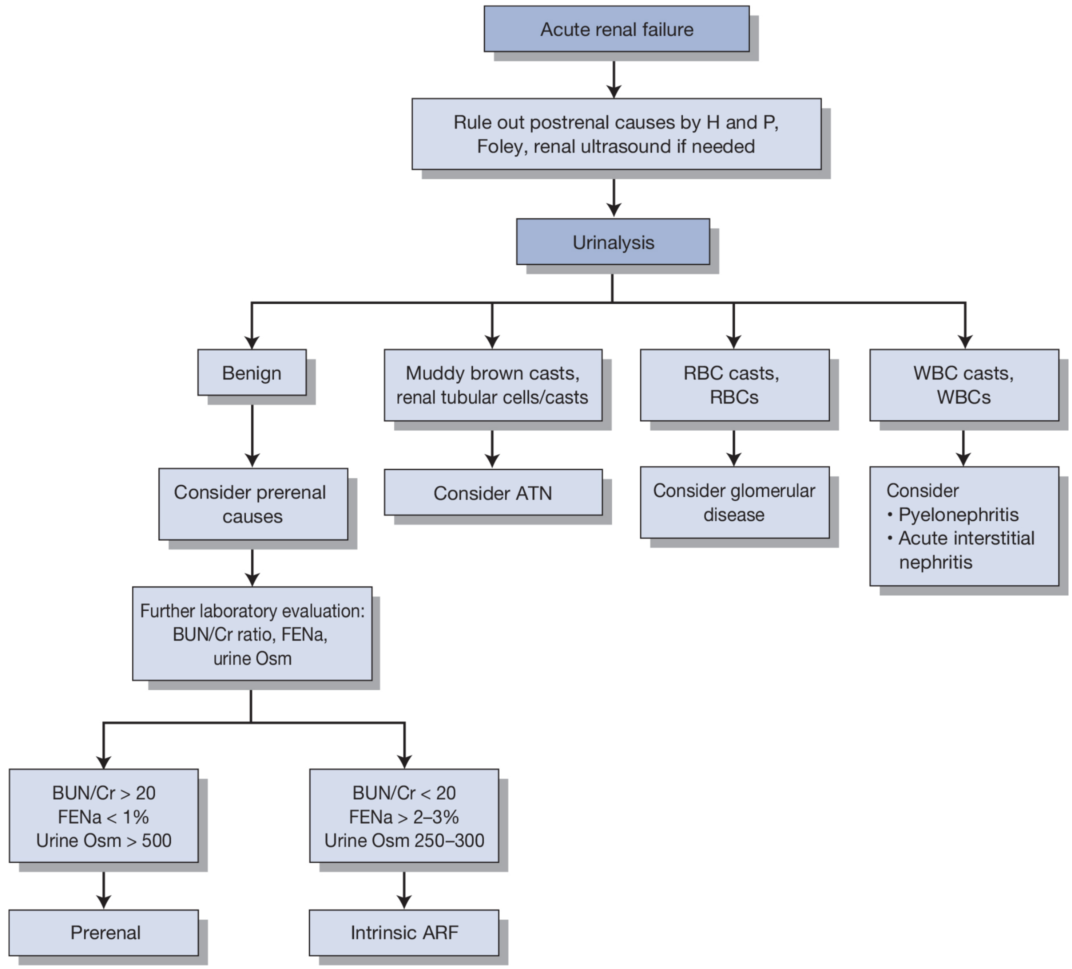


FIGURE 7-2 **Evaluation of AKI.**

2. Metabolic
   a. **Hyperkalemia**—due to decreased excretion of K+ and the movement of potassium from ICF to ECF due to tissue destruction and acidosis
   b. **Metabolic acidosis** (with increased anion gap)—due to decreased excretion of hydrogen ions; if severe (below 16 mEq/L), correct with sodium bicarbonate
   c. Hypocalcemia—loss of ability to form active vitamin D and rapid development of PTH resistance
   d. Hyponatremia may occur if water intake is greater than body losses, or if a volume-depleted patient consumes excessive hypotonic solutions. (Hypernatremia may also be seen in hypovolemic states.)
   e. Hyperphosphatemia—due to decreased clearance

f. Hyperuricemia

Quick HIT

In the early phase of AKI, the most common mortal complications are hyperkalemic cardiac arrest and pulmonary edema.

TABLE 7-2 Urinalysis Findings in Renal Failure

Cause	Urine Sediment	Protein	Blood
Prerenal	Benign sediment—few hyaline casts	Negative	Negative
Intrarenal			
Acute tubular necrosis	"Muddy brown" casts, renal tubular cells/casts, granular casts	Trace	Negative
Acute glomerulonephritis	Dysmorphic RBCs, RBCs with casts, WBCs with casts, fatty casts	4+	3+
Acute interstitial nephritis	RBCs, WBCs, WBCs with casts, eosinophils	1+	2+
Postrenal	Benign; may or may not see RBCs, WBCs	Negative	Negative

3. Uremia—toxic end products of metabolism accumulate (especially from protein metabolism), leading to such complications as:
   a. Platelet dysfunction
   b. Immune dysfunction
   c. Pericarditis
   d. Encephalopathy
4. Infection
   a. A common and serious complication of AKI (occurs in 50% to 60% of cases). The cause is probably multifactorial, but uremia itself is thought to impair immune function.
   b. Examples include pneumonia, UTI, wound infection, and sepsis.

E. Treatment

1. General measures (see also Table 7-3)

a. Avoid medications that decrease renal blood flow (NSAIDs) and/or that are nephrotoxic (e.g., aminoglycosides, radiocontrast agents)
b. Adjust medication dosages for level of renal function
c. Correct fluid imbalance
   - If volume depleted, give IV fluids. However, many patients with AKI are volume overloaded (especially if they are oliguric or anuric), so diuresis may be necessary.
   - The goal is to strike a balance between correcting volume deficits and avoiding volume overload (while maintaining adequate urine output). Remember that urine output is a reflection of renal blood flow (volume status) and GFR (kidney function).
   - Monitor fluid balance by daily weight measurements (most accurate estimate) and intake–output records.
   - Be sure to take into account the patient's cardiac history when considering treatment options for fluid imbalances (i.e., give fluid cautiously to a patient with CHF).
d. Correct electrolyte disturbances if present
e. Optimize cardiac output. BP should be approximately 120–140/80–90
f. Indications for urgent dialysis often remembered by "AEIOU" mnemonic: Acidosis, Electrolytes, Intoxications (such as in overdoses), volume Overload, Uremia

2. Prerenal
   a. Treat the underlying disorder (such as hypovolemic or cardiogenic shock).
   b. Give fluids to maintain euvolemia and restore blood pressure—do not give to patients with edema or ascites. May be necessary to stop antihypertensive medications. Remember that NS is often preferred unless acidemia is present (may worsen with hyperchloremia), in which case LR can be used.
   c. Eliminate any offending agents (ACE inhibitors, NSAIDs).

TABLE 7-3 Prognostic Factors in AKI

Severity of renal failure	Magnitude of increase in Cr Presence of oliguria Fractional excretion of sodium Requirement for dialysis Duration of severe renal failure Marked abnormalities on urinalysis
Underlying health of patient	Age Presence, severity, and reversibility of underlying disease
Clinical circumstances	Cause of renal failure Severity and reversibility of acute process(es) Number and type of other failed organ systems Development of sepsis and other complications

Adapted with permission from Schrier RW, ed. *Diseases of the Kidney and Urinary Tract*. Vol II. 7th ed. Lippincott Williams & Wilkins; 2001:1128. Table 41-14.

TABLE 7-4 Differentiation of AKI Versus CKD

Favors Chronic	Favors Acute
History of kidney disease, HTN, abnormal urinalysis, edema	—
Small kidney size on renal ultrasound	—
—	Return of renal function to normal with time
Hyperkalemia, acidemia, hyperphosphatemia, anemia	Hyperkalemia, acidemia, hyperphosphatemia, anemia
—	Urine output <500 mL/day without uremic symptoms
Urinalysis with broad casts (i.e., more than two to three WBCs in diameter)	—

Adapted with permission from Schrier RW, ed. *Diseases of the Kidney and Urinary Tract*. Vol II. 7th ed. Lippincott Williams & Wilkins; 2001:1098. Figure 41-5.

3. Intrinsic
   a. Once ATN develops, therapy is supportive and renal function generally recovers. Eliminate the cause/offending agent.

4. Postrenal—a bladder catheter may be inserted to decompress the urinary tract. Consider urology consultation
   a. Be aware of the potential for postobstructive diuresis and a rapid increase in urine output when obstruction is resolved, which may require IV fluid replacement.

Quick HIT

Contrast-induced nephropathy is now controversial.

Quick HIT

Whenever a patient has elevated Cr levels, the first thing to do is to look at previous laboratory data to determine the patient's **baseline** Cr level, if possible. This helps determine whether the patient has AKI, CKD, or chronic renal insufficiency/failure with superimposed AKI. (This condition is known as "acute on chronic" renal failure.)

Quick HIT

- **Azotemia** refers to the elevation of BUN.
- **Uremia** refers to the signs and symptoms associated with accumulation of nitrogenous wastes due to impaired renal function. It is difficult to predict when uremic symptoms will appear, but it rarely occurs unless the BUN is >60 mg/dL.

Chronic Kidney Disease

A. General Characteristics

1. Chronic kidney disease (CKD) is defined as either decreased kidney function (GFR <60 mL/min) or kidney damage (structural or functional abnormalities) for at least 3 months, regardless of cause (see also Tables 7-4 and 7-5).
2. Causes
   a. **Diabetes is the most common cause** (30% of cases).

b. **HTN is responsible for 25% of cases.**
c. Chronic GN accounts for 15% of cases.
d. Interstitial nephritis, polycystic kidney disease, obstructive uropathy.
e. Any of the causes of AKI may lead to CKD if prolonged and/or if treatment is delayed.

TABLE 7-5 Stages of CKD

CKD Stage	GFR
1	≥90
2	60–89
3a	45–59
3b	30–44
4	15–29
5	<15

3. Pathophysiology
   a. Plasma Cr varies inversely with GFR.
   b. Cr clearance is the most common clinical measure of GFR (although remember this is an indirect estimation and can lead to miscalculations).
   c. An increase in plasma Cr indicates disease progression, whereas a decrease suggests recovery of renal function (assuming muscle mass has not changed). Most laboratories now also report an estimated GFR (eGFR) each time the creatinine is ordered.
4. Prevalence is increasing, and incidence is highest in African American patients.

Quick HIT

Diabetes and hypertension are the most common causes of ESRD.

Quick HIT

ESRD is not defined by BUN or creatinine levels. It is classically a loss of kidney function that leads to laboratory and clinical findings of uremia. Newer definitions use CrCl to estimate GFR (CrCl <15 mL/min distinguished as ESRD).

B. Clinical Features—any of the following may be present:

1. Cardiovascular
   a. HTN
      - Secondary to salt and water retention—decreased GFR stimulates renin–angiotensin system and aldosterone secretion to increase, which leads to an increase in BP.
      - Renal failure is the most common cause of secondary HTN.

   b. CHF—due to volume overload, HTN, and anemia
   c. Pericarditis (uremic)
2. GI (usually due to uremia)
   a. Nausea, vomiting
   b. Loss of appetite (anorexia)
3. Neurologic
   a. Symptoms include lethargy, somnolence, confusion, peripheral neuropathy, and uremic seizures. Physical findings include weakness, asterixis, and hyperreflexia. Patients may show “restless legs”—neuropathic pain in the legs that is only relieved with movement.
   b. Hypocalcemia (from decreased vitamin D conversion) can cause lethargy, confusion, and tetany.
4. Hematologic
   a. Normocytic normochromic anemia (secondary to deficiency of erythropoietin)—may be severe.
   b. Bleeding secondary to platelet dysfunction (due to uremia). Platelets do not degranulate in uremic environment.
5. Endocrine/metabolic
   a. Calcium–phosphorus disturbances
      - Decreased renal clearance of phosphate leads to **hyperphosphatemia**, which results in decreased renal production

of 1,25-dihydroxy vitamin D. This leads to **hypocalcemia**, which causes secondary hyperparathyroidism.

- So, **hypo**calcemia and **hyper**phosphatemia are usually seen, but long-standing secondary hyperparathyroidism and calcium-based phosphate binders may sometimes cause **hypercalcemia.** This can be due to a parathyroid gland secreting excess PTH without responsiveness to plasma calcium levels, known as **tertiary hyperparathyroidism.**
- Secondary hyperparathyroidism causes **renal osteodystrophy**, which causes weakening of bones and possibly fractures.
- Hyperphosphatemia may cause calcium and phosphate to precipitate, which causes vascular calcifications that may result in necrotic skin lesions. This is called **calciphylaxis** and is usually irreversible.

b. Sexual/reproductive symptoms due to hypothalamic–pituitary disturbances and gonadal response to sex hormones: in men, decreased testosterone; in women, amenorrhea, infertility, and hyperprolactinemia.

c. Pruritus (multifactorial etiology)—common and difficult to treat. Dialysis and ultraviolet light.

Quick HIT

Increased susceptibility to infections is a major cause of mortality in patients with CKD.

Quick HIT

Hypocalcemia leads to secondary hyperparathyroidism, which removes calcium from bones, making them weak and susceptible to fracture.

6. Fluid and electrolyte problems (see Chapter 8).
   a. Volume overload—watch for pulmonary edema
   b. Hyperkalemia—due to decreased urinary secretion
   c. Hypermagnesemia—occurs secondary to reduced urinary loss
   d. Hyperphosphatemia—see above

e. Metabolic acidosis—due to loss of renal mass (and thus decreased production of ammonia, which the kidneys use to buffer excreted acid) and the kidney's inability to excrete H+ itself.

7. Immunologic—uremia inhibits cellular and humoral immunity.

C. Diagnosis

1. Urinalysis—examine sediment (see AKI)
   a. Level of proteinuria is increasingly being reported alongside GFR as it is associated with more rapid progression of CKD
2. Measure Cr clearance to estimate GFR
3. CBC (anemia, thrombocytopenia)
4. Serum electrolytes (e.g., K^+, Ca^{2+}, PO_4^{3-}, serum protein)
5. Renal ultrasound—evaluate size of kidneys/rule out obstruction
   a. Small kidneys are suggestive of chronic renal insufficiency with little chance of recovery
   b. Presence of normal-sized or large kidneys does not exclude CKD
   c. Renal biopsy—in select cases to determine specific etiology

Quick HIT

In a patient with CKD, symptomatic volume overload and severe hyperkalemia are the most common complications that require urgent intervention.

Quick HIT

Life-Threatening Complications in CKD

- Hyperkalemia—obtain an ECG (be aware that potassium levels can be high without ECG changes).
- Pulmonary edema secondary to volume overload—look for recent weight gain.
- Infection (e.g., pneumonia, UTI, sepsis).

D. Treatment

1. Diet

a. Low protein—0.7 to 0.8 g/kg body weight per day. This may slow the progression of CKD.
b. Use a low-salt diet if HTN, CHF, or oliguria are present.
c. Restrict potassium, phosphate, and magnesium intake.

2. ACE inhibitors—dilate efferent arteriole of glomerulus
   a. If used early on, they reduce the risk of progression to ESRD because they slow the progression of proteinuria.
   b. Use with great caution because they can cause hyperkalemia.
3. BP control
   a. Strict control decreases the rate of disease progression.
   b. ACE inhibitors are the preferred agents. Multiple drugs, including diuretics, may be required.
4. Glycemic control (if the patient is diabetic) prevents worsening of proteinuria
5. Smoking cessation has been associated with slower rates of progression
6. Correction of electrolyte abnormalities
   a. Correct hyperphosphatemia with calcium citrate (a phosphate binder).
   b. Patients with chronic renal disease are generally treated with long-term oral calcium and vitamin D in an effort to prevent secondary hyperparathyroidism and uremic osteodystrophy.
   c. Acidosis—treat the underlying cause (renal failure). Patients may require oral bicarbonate replacement.
7. Anemia—treat with erythropoietin, which kidneys normally secrete
8. Volume overload, pulmonary edema—diuretics (furosemide) early on, titrate the dose to achieve an appropriate increase in urine output. If lack of response, will likely need dialysis
9. Pruritus—try capsaicin cream or cholestyramine and UV light
10. Dialysis (see indications in the Dialysis section)
11. Transplantation is the only cure

Dialysis

A. General Characteristics

1. Overview

a. Dialysis is the artificial mechanism by which fluid and toxic solutes are removed from the circulation when the kidneys cannot do so sufficiently.
b. In all forms of dialysis, the blood interfaces with an artificial solution resembling human plasma (called the dialysate), and diffusion of fluid and solutes occurs across a semipermeable membrane.
c. **The two major methods of dialyzing a patient are hemodialysis and peritoneal dialysis** (discussed below).
d. The majority of dialysis patients in the United States receive hemodialysis at hospitals or dialysis centers, but more and more patients are opting for chronic ambulatory peritoneal dialysis (CAPD).
e. For critically ill patients requiring emergent dialysis, continuous renal replacement therapy (CRRT) can be used for constant renal support. This also avoids the larger fluid shifts of intermittent hemodialysis which hemodynamically unstable or heart failure patients may not be able to handle.

***Quick* HIT**

Indications for Dialysis

- **A**cidosis—significant, intractable metabolic acidosis
- **E**lectrolytes—severe, persistent hyperkalemia
- **I**ntoxications—methanol, ethylene glycol, lithium, aspirin
- **O**verload—hypervolemia not managed by other means
- **U**remia (severe)—based on clinical presentation, not laboratory values (e.g., uremic pericarditis or encephalopathy are absolute indications for dialysis)

B. When to Initiate Dialysis

1. General settings in which dialysis is considered.
   a. CKD—dialysis serves as a bridge to renal transplantation or as a permanent treatment when the patient is not a transplantation candidate.
   b. AKI—dialysis is often required as a temporary measure until the patient's renal function improves, often due to absolute indications

(see Quick Hit).

c. Overdose of medications or ingestions of substances cleared by the kidneys—some, but not all medications and toxins can be dialyzed (see Quick Hit).

2. Nonemergent indications
   a. Note: Cr and BUN levels are **not** absolute indications for dialysis, however some nephrologists will decide to initiate dialysis once a CKD patient's GFR drops below a certain value
   b. Symptoms of uremia
      - Nausea and vomiting
      - Lethargy/deterioration in mental status, encephalopathy, seizures
      - Pericarditis
3. Emergent indications (usually in the setting of renal failure)
   a. Life-threatening manifestations of volume overload
      - Pulmonary edema
      - Hypertensive emergency refractory to antihypertensive agents
   b. Severe, refractory electrolyte disturbances, for example, hyperkalemia, hypermagnesemia
   c. Severe metabolic acidosis
   d. Drug toxicity/ingestions (particularly in patients with renal failure): methanol, ethylene glycol, lithium, aspirin

Quick HIT

Creatinine level is not an absolute indication for dialysis.

C. Hemodialysis

1. Process
   a. The patient's blood is pumped by an artificial pump outside of the body through the dialyzer, which typically consists of fine capillary networks of semipermeable membranes. The dialysate flows on the outside of these networks, and fluid and solutes diffuse across the membrane.
   b. The patient's blood must be heparinized to prevent clotting in the dialyzer.

2. Frequency: Most hemodialysis patients require 3 to 5 hours of dialysis 3 days per week
3. Access
   a. Use the central catheter placed using the Seldinger technique most often in the subclavian or jugular vein for temporary access
   b. Tunneled catheters are placed under the skin which leads to a lower rate of infection. These catheters are often suitable for use up to 6 months
   c. Arteriovenous fistula
      - Best form of permanent dialysis access.
      - It requires vascular surgery to connect the radial or brachial artery to veins in the forearm.
      - An audible bruit and palpable thrill (due to high flow) over the fistula indicates that it is patent. Absence of these findings is abnormal and is concerning for thrombosis of the vessel.
   d. An alternative to an arteriovenous fistula is an implantable graft—typically made of polytetrafluoroethylene (PTFE)
4. Alternatives to traditional hemodialysis
   a. Continuous arteriovenous hemodialysis (CAVHD) and continuous venovenous hemodialysis (CVVHD) are often used in hemodynamically unstable patients, such as ICU patients with AKI. This allows for closer control of electrolytes and fluid status.
   b. Lower flow rates of blood and dialysate enable dialysis to occur while minimizing rapid shifts in volume and osmolality which these patients may not be able to tolerate.
   c. They require highly efficient dialyzers to be effective.
5. Advantages of hemodialysis
   a. It is more efficient than peritoneal dialysis. High flow rates and efficient dialyzers shorten the period of time required for dialysis.
   b. It can be initiated more quickly than peritoneal dialysis, using temporary vascular access in the emergent setting.
6. Disadvantages of hemodialysis
   a. It is less similar to the physiology of natural kidney function than is peritoneal dialysis, predisposing the patient to the following:
      - Hypotension due to rapid removal of intravascular volume leading to rapid fluid shifts from the extravascular space into cells.

- Hypo-osmolality due to solute removal.

b. Requires vascular access

D. Peritoneal Dialysis

1. Process
   a. The peritoneum serves as the dialysis membrane. Dialysate fluid is infused into the peritoneal cavity, then fluids and solutes from the peritoneal capillaries diffuse into the dialysate fluid, which is drained from the abdomen.
   b. A **hyperosmolar** (high-glucose) solution is used, and water is removed from the blood via osmosis.
2. Frequency: dialysate fluid is drained and replaced every hour in acute peritoneal dialysis, but only once every 4 to 8 hours in CAPD.
3. Access
   a. With CAPD, dialysate is infused into the peritoneal fluid via an implanted catheter.
   b. A temporary catheter is used for acute peritoneal dialysis.
4. Advantages
   a. The patient can learn to perform dialysis on their own.
   b. It mimics the physiology of normal kidney function more closely than hemodialysis in that it is more continuous.
5. Disadvantages
   a. High glucose load may lead to hyperglycemia and hypertriglyceridemia.
   b. Peritonitis is a significant potential complication.
   c. The patients must be highly motivated to self-administer it.
   d. Cosmetic—there is increased abdominal girth due to dialysate fluid.

E. Limitations and Complications of Dialysis

1. Limitations—dialysis does not replicate the kidney's synthetic functions. Therefore, dialysis patients are still prone to erythropoietin and vitamin D deficiency, with their associated complications.
2. Complications associated with hemodialysis
   a. Hypotension—may result in myocardial ischemia, fatigue, and so on
   b. The relative hypo-osmolality of the ECF compared with the brain may result in nausea, vomiting, headache, and rarely, seizures or

coma

c. "First-use syndrome"—chest pain, back pain, and rarely, anaphylaxis may occur immediately after a patient uses a new dialysis machine

d. Hemolysis: often due to issues with dialysate solution

e. Complications associated with anticoagulation—hemorrhage, hematoma, etc.

f. Infection of vascular access site—may lead to sepsis

g. Hemodialysis-associated amyloidosis of β_2-microglobulin in bones and joints, can lead to bilateral carpal tunnel syndrome

3. Complications associated with peritoneal dialysis
   a. Peritonitis, often accompanied by fever and abdominal pain—usually can be treated with intraperitoneal antibiotics; cloudy peritoneal fluid is key sign
   b. Abdominal/inguinal hernia—increased risk due to elevated intra-abdominal pressures
   c. Hyperglycemia—especially with diabetic patients
   d. Protein malnutrition

Proteinuria and Hematuria

Proteinuria

A. General Characteristics

1. Defined as the urinary excretion of >150 mg protein/24 hours
2. Classification
   a. Glomerular
      - Due to increased glomerular permeability to proteins from various causes
      - Can lead to nephrotic syndrome (see below)
      - May be seen in all types of GN
      - Protein loss tends to be more severe than in nonglomerular causes

   b. Tubular
      - Small proteins normally filtered at the glomerulus then reabsorbed by the tubules appear in the urine because of abnormal tubules

(i.e., due to decreased tubular reabsorption).
- Proteinuria and kidney damage tends to be less severe due to a lower quantity and nephrotoxicity of the associated proteins.
- Causes include sickle cell disease, urinary tract obstruction, and interstitial nephritis.

c. Overflow proteinuria—increased production of small proteins overwhelms the tubules' ability to reabsorb them (e.g., Bence Jones protein in multiple myeloma, myoglobin in rhabdomyolysis)

d. Other causes of proteinuria (all of the following can affect renal blood flow):
- UTI
- Fever, heavy exertion/stress, CHF
- Pregnancy
- Orthostatic proteinuria—occurs when the patient is standing but not when recumbent; self-limited and benign

Quick HIT

Asymptomatic Proteinuria

- Asymptomatic transient proteinuria has an excellent prognosis (no further evaluation necessary). Often due to fever or exercise.
- Asymptomatic **persistent** proteinuria and symptomatic proteinuria require further workup (high chance of renal disease in these patients).

3. Nephrotic syndrome

a. Key features
- **Urine protein** excretion rate >3.5 g/24 hours.
- **Hypoalbuminemia**—hepatic albumin synthesis cannot keep up with these urinary protein losses. The result is decreased plasma oncotic pressure, which leads to edema.
- **Edema**—this is often the initial complaint (from pedal edema to periorbital to anasarca, ascites, pleural effusion), and results from hypoalbuminemia. Increased aldosterone secretion exacerbates the problem (increases sodium reabsorption).
- **Hyperlipidemia** and lipiduria—increased hepatic synthesis of LDL and VLDL because liver is revving up albumin synthesis.

- Hypercoagulable state (due to loss of certain anticoagulants in the urine)—increased risk of thromboembolic events (deep venous thrombosis, pulmonary embolism, renal vein thrombosis).
- Increased incidence of infection—results from loss of immunoglobulins in the urine, particularly susceptible to pneumococcal infections.

b. Nephrotic syndrome usually indicates significant glomerular disease (either primary or secondary to systemic illness) as the underlying cause is abnormal glomerular permeability.

c. Causes
- Primary glomerular disease (50% to 75% of cases of nephrotic syndrome)—membranous nephropathy is most common in adults (40% of cases), followed by focal segmental glomerulosclerosis (FSGS) (35%) and membranoproliferative GN (15%). Minimal change disease (MCD) is the most common cause in children (75% of cases).
- Secondary glomerular pathology:
- Systemic disease—diabetes, collagen vascular disease, SLE, RA, Henoch–Schönlein purpura, polyarteritis nodosa (PAN), granulomatosis with polyangiitis
- Amyloidosis, cryoglobulinemia
- Drugs/toxins—captopril, heroin, heavy metals, NSAIDs, penicillamine
- Infection—bacterial, viral, protozoal
- Multiple myeloma, malignant HTN, transplant rejection

***Quick* HIT**

Four Key Features of Nephrotic Syndrome

- Proteinuria
- Hypoalbuminemia
- Hyperlipidemia
- Edema

A 43-year-old Caucasian man comes to the physician because of fatigue and body swelling that has developed over the last few weeks. He has no significant medical history, and takes no medications. He does not smoke or drink alcohol, and exercises 3 times weekly. He is afebrile with a blood pressure of 128/86 mmHg, heart rate of 88 beats per minute, and respiratory rate of 16 breaths per minute. On physical examination, there is noticeable periorbital edema with diffuse edema of the extremities. His laboratory values are shown below.

Sodium	138 mEq/L
Potassium	4.5 mEq/L
Chloride	104 mEq/L
Bicarbonate	24 mEq/L
Blood urea nitrogen	8 mg/dL
Creatinine	0.9 mg/dL
Glucose	146 mg/dL
Albumin	2.8 g/dL
Urine dipstick	3+ protein

Which of the following is also likely to be present in this patient?

A. HIV infection
B. Hypercholesterolemia
C. S3 on cardiac auscultation
D. Hematuria

- **The answer is B: Hypercholesterolemia.** This patient has three characteristics of nephrotic syndrome: proteinuria, hypoalbuminemia, and generalized edema. Nephrotic range proteinuria must be confirmed with a 24-hour urine sample and is

defined as >3.5 g/d. Another important characteristic of nephrotic syndrome is hyperlipidemia. In response to the reduction in plasma oncotic pressure due to the loss of albumin and other plasma proteins in the urine, the liver increases synthesis of lipoproteins resulting in hypercholesterolemia. In addition, there is impaired liver metabolism that often results in hypertriglyceridemia. Finally, lipiduria may also be present and is manifested as urine fatty casts with a “Maltese cross” appearance. **(A)** FSGS is the most common glomerulopathy in the setting of HIV infection. However, this patient does not have apparent risk factors for HIV infection and he better fits the epidemiologic profile of membranous nephropathy (middle-aged Caucasian). **(C)** This patient has characteristics of nephrotic syndrome and therefore heart failure is not the correct diagnosis. **(D)** Though there is some overlap of nephrotic and nephritic syndromes, as well as the causes of each, hematuria is typically a feature of nephritic syndrome. There are typically few or no cells in the urine of nephrotic patients.

CLINICAL PEARL 7-6

Urinalysis

Collection—a clean-catch, midstream urine sample (after cleaning urethral meatus) is usually adequate for urinalysis and urine culture in adults.

Urinalysis consists of the following three steps:

- Visual inspection of urine—examine color, clarity
- Dipstick reactions
  - pH—this depends on acid–base status. The average is about 6, but can range from 4.5 to 8.0.
  - Specific gravity—this is directly proportional to urine osmolality (and therefore solute concentration in urine). Normal is 1.002 to 1.035. It increases with volume depletion and decreases with volume overload. Appropriate changes in specific gravity with volume status of the patient indicate adequate tubular function (i.e., renal concentrating ability).
  - Protein—proteinuria is defined as >150 mg/day; nephrotic syndrome, >3.5 g/day. The following are rough guidelines: Trace = 50 to 150 mg/day; 1+ = 150 to 500 mg/day; 2+ = 0.5 to 1.5 g/day; 3+ = 2 to 5 g/day; 4+ = >5 g/day.
  - Glucose—excessive glucose indicates diabetes. Absence of glucosuria does **not** rule out diabetes, however.
  - Blood—hematuria—see text
  - Ketones—DKA, starvation
  - Nitrite—suggests presence of bacteria in urine, usually GNR
  - Leukocyte esterase—suggests presence of WBC in urine; if negative, infection is unlikely
- Microscopic examination of urine sediment
- Look for casts, cells, bacteria, WBCs, RBCs (number, shape), crystals.

B. Diagnosis

1. Urine dipstick test (read color changes)
   a. Specific for albumin—detects concentrations of 30 mg/dL or higher
   b. Graded 0, trace, 1+ (15 to 30 mg/dL) through 4+ (>500 mg/dL)
   c. More sensitive to albumin than to immunoglobulins, thus can lead to false-negative results when predominant urinary protein is globulin (e.g., light chains in myeloma)
2. Urinalysis (see Clinical Pearl 7-6)
   a. Initial test once proteinuria is detected by dipstick test
   b. Examination of urine sediment is important
      - RBC casts suggest GN.

- WBC casts suggest pyelonephritis and interstitial nephritis.
- Fatty casts suggest nephrotic syndrome (lipiduria).

c. If urinalysis confirms the presence of protein, a 24-hour urine collection (for albumin and Cr) is appropriate to establish the presence of significant proteinuria.

3. Test for microalbuminuria
   a. Corresponds to albumin excretion of 30 to 300 mg/day.
   b. This is below the range of sensitivity of standard dipsticks. Special dipsticks can detect microgram amounts of albumin. If the test result is positive, perform a radioimmunoassay (the most sensitive and specific test for microalbuminuria).
   c. **Microalbuminuria can be an early sign of diabetic nephropathy and often presents before any other laboratory abnormalities or overt signs or symptoms.**
4. Other tests to determine etiology (may or may not be necessary depending on case)
   a. Renal ultrasound—to detect obstruction, masses, cystic disease
   b. Intravenous pyelogram (IVP)—to detect chronic pyelonephritis
   c. Immunologic tests: ANA levels (lupus), antiglomerular basement membrane (Goodpasture syndrome), hepatitis serology (causes of MN, MPGN), antistreptococcal antibody titers (PSGN), complement levels, cryoglobulin studies
   d. Serum and urine electrophoresis (myeloma)
   e. Renal biopsy—if no cause is identified by less invasive means

C. Treatment

1. Asymptomatic proteinuria
   a. If it is transient, no further workup or treatment is necessary.
   b. If it is persistent, further testing is indicated. Start by checking BP and examining urine sediment. Treat the underlying condition and associated problems (e.g., hyperlipidemia).
2. Symptomatic proteinuria—further testing is always required
   a. Treat the underlying disease (diabetes, multiple myeloma, SLE, MCD).
   b. ACE inhibitors (ARB cannot tolerate ACE)—these decrease urinary albumin loss. They are an essential part of treatment for diabetics

with HTN and should be started before fixed albuminuria is present.

c. Diuretics—if edema is present.
d. Limit dietary protein and sodium.
e. Treat hypercholesterolemia (using diet or a lipid-lowering agent).
f. Anticoagulation if thrombosis occurs. Currently, there is not enough data to support routine prophylactic anticoagulation of these patients and must be considered on a case-by-case basis.
g. Vaccinate against influenza and pneumococcus—there is an increased risk of infection in these patients.

Quick HIT

Gross hematuria is a common presenting sign in patients with bladder cancer (up to 85% of cases) and patients with renal cell carcinoma (up to 40% of cases).

Quick HIT

Infection (cystitis, urethritis, prostatitis) accounts for 25% and stones for 20% of all cases of atraumatic hematuria.

Hematuria

A. General Characteristics

1. Hematuria is defined as >3 erythrocytes/HPF on urinalysis.
2. Microscopic hematuria is more commonly glomerular in origin; gross hematuria is more commonly nonglomerular or urologic in origin.
3. **Persistent hematuria in adults should include a workup for bladder or kidney cancer.**
4. This may lead to obstruction if large clots form in the lower GU tract (potentially requiring bladder catheterization and irrigation). Excessive blood loss can lead to iron-deficiency anemia.

B. Causes

1. Intrarenal

a. Tumor (RCC), infection (pyelonephritis, abscess), stones, and trauma
b. Glomerular disease, immunoglobulin A nephropathy
c. Strenuous exercise (marathon running), fever—hematuria is generally harmless
d. Polycystic kidney disease, simple cysts
e. Sickle cell disease
f. Analgesic nephropathy (renal papillary necrosis and chronic interstitial nephritis)
g. Renal papillary necrosis

2. Ureter
   a. Tumor, infection (pyelonephritis), stones, and trauma
   b. Stricture
3. Lower urinary tract (bladder, urethra, prostate)
   a. Tumor (bladder, prostate), infection (cystitis, prostatitis), stones, and trauma (Foley placement, invasive procedures)
   b. BPH—rarely causes isolated hematuria
   c. Chronic irritation
4. Other
   a. Systemic diseases (SLE, rheumatic fever, Henoch–Schönlein purpura, granulomatosis with polyangiitis, HUS, Goodpasture syndrome, PAN)
   b. Bleeding disorders (e.g., hemophilia, thrombocytopenia)
   c. Medications (cyclophosphamide, anticoagulants, salicylates, sulfonamides)

Quick HIT

Menstrual blood can contaminate a urine sample and lead to a false-positive dipstick reading for hematuria.

Quick HIT

If hematuria is microscopic, think of glomerular disease. If gross, think of postrenal causes (trauma, stones, malignancy). Infection can cause either gross or microscopic hematuria.

C. Diagnosis

1. Urine dipstick—sensitivity in identifying hematuria is >90% (Figure 7-3)
2. Urinalysis—crucial in evaluation of hematuria
   a. Examine urine sediment—this is very important in identifying possible renal disease.
   b. If RBC casts and proteinuria are also present, a glomerular cause is almost always present (usually GN)
   c. If pyuria is present, send for urine culture
   d. If dipstick is positive for blood, but urinalysis does not reveal microscopic hematuria (no RBCs), hemoglobinuria or myoglobinuria (as in rhabdomyolysis) is likely present

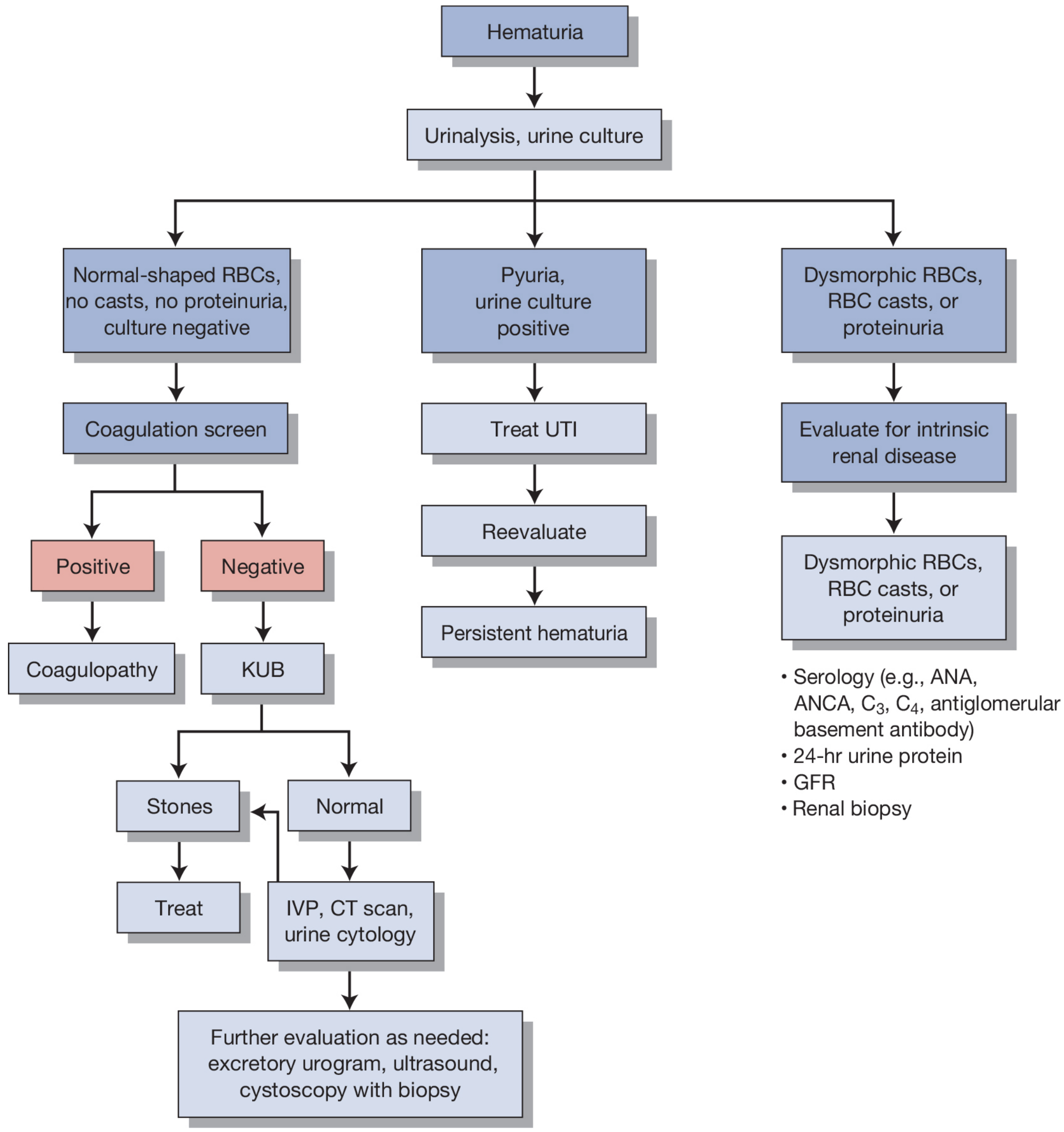


FIGURE 7-3 **Evaluation of hematuria.**

Quick HIT

If the patient has no other symptoms associated with hematuria, and thorough workup fails to reveal a cause, the prognosis is excellent.

3. Urine specimen—for cytology
   a. To detect cancers (bladder cancer is the main concern). This test has a low sensitivity.

b. **If suspicion for malignancy is high, perform a cystoscopy to evaluate the bladder regardless of cytology results. This is a necessity in nearly all patients over 40 or those with risk factors for bladder cancer.**

4. Twenty-four–hour urine—test for Cr and protein to assess renal function. Collect if proteinuria is present. (If it is heavy, glomerular disease is likely.)
5. Blood tests—coagulation studies, CBC, BUN/Cr
6. IVP, CT scan, ultrasound—if no cause is identified by the above tests; look for stones, tumors, cysts, ureteral strictures, or vascular malformations
7. Renal biopsy—if there is suspicion of glomerular disease.

D. Treatment

Treat the underlying cause.

Glomerular Disease

Overview

A. General Characteristics

1. Can be primary (intrinsic renal pathology) or secondary (to a systemic disease). Two important categories of glomerular pathology are diseases that present with nephrotic syndrome and those that present with nephritic syndrome. Many conditions have features of both. See Table 7-6.
2. There is a wide range in the rate of disease progression, varying from days to weeks in the acute glomerular diseases, to years in the chronic disorders.

B. Causes

1. GN is usually caused by immune-mediated mechanisms.
2. Other mechanisms include metabolic and hemodynamic disturbances.

Quick HIT

Rapid progressive GN is a clinical syndrome that includes any type of GN in which rapid deterioration of renal function occurs over weeks to months, leading to renal failure and ESRD.

Quick HIT

Possible Presentations of Glomerular Disease

- Isolated proteinuria
- Isolated hematuria
- Nephritic syndrome—hematuria, HTN, azotemia
- Nephrotic syndrome—proteinuria, edema, hypoalbuminemia, hyperlipidemia

C. Clinical Features

1. Glomerular disorders are characterized by impairment in selective filtration of blood, resulting in excretion of larger substances such as plasma proteins and blood cells. As disease advances, GFR decreases proportionately, leading to renal failure and the possible need for dialysis and/or transplantation.
2. The classic features are proteinuria, hematuria, or both. Nephrotic range proteinuria is pathognomonic for glomerular disease.

D. Diagnosis

1. Urinalysis (hematuria, proteinuria, RBC casts)
2. Blood tests (renal function tests)
3. Needle biopsy of the kidney

E. Treatment depends on the disease, but often involves steroids and cytotoxic agents.

Primary Glomerular Disorders (see Figure 7-4)

A. Minimal Change Disease

1. Nephrotic syndrome—most common presentation (see also Clinical Pearl 7-7).
2. Most common in children—Hodgkin disease and non-Hodgkin lymphoma have been associated with MCD.
3. No histologic abnormalities on light microscopy; **fusion/effacement of foot processes on electron microscopy.**
4. Excellent prognosis; responsive to steroid therapy (4 to 8 weeks), although relapses may occur.
5. Current evidence points to systemic T-cell dysfunction as the most likely root cause of MCD.

TABLE 7-6 Nephritic Versus Nephrotic Syndrome

	Nephritic Syndrome	Nephrotic Syndrome
Pathogenesis	Inflammation of glomeruli due to any of the causes of glomerulonephritis	Abnormal glomerular permeability due to a number of conditions
Causes	Poststreptococcal glomerulonephritis is the most common cause, but may be due to any of the causes of glomerulonephritis	Many conditions. Membranous glomerulonephritis is the most common cause in adults. Other causes include diabetes, SLE, drugs, infection, glomerulonephritis (focal segmental and others). Minimal change disease is the most common cause in children
Laboratory Findings	Hematuria AKI—azotemia, oliguria Proteinuria, if present, is mild and not in nephrotic range	Urine protein excretion rate >3.5 g/24 hr Hypoalbuminemia Hyperlipidemia, fatty casts in urine
Clinical Findings	HTN Edema	Edema Hypercoagulable state Increased risk of infection

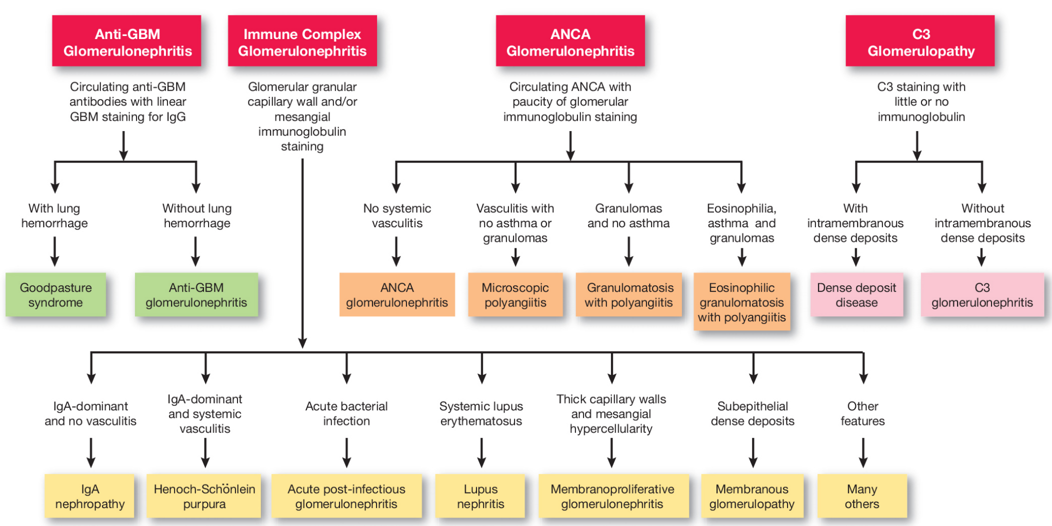


FIGURE 7-4 **Algorithm for glomerulonephritis.**

B. Focal Segmental Glomerulosclerosis

1. A histopathologic lesion which is the result of a wide range of disease processes.
2. This accounts for 25% of cases of nephrotic syndrome in adults and is more common in blacks. Hematuria and HTN are often present.
3. It has a fair to poor prognosis. It is generally resistant to steroid therapy—patients develop renal insufficiency within 5 to 10 years of diagnosis. The course is progressive to ESRD.
4. The treatment regimen is controversial, but remission has been achieved in 50% of patients with the use of cytotoxic agents, steroids, and immunosuppressive agents. ACE/ARBs are also commonly indicated.

C. Membranous Glomerulonephritis

1. Usually presents with nephrotic syndrome; glomerular capillary walls are thickened. Most common nephrotic syndrome in nondiabetic adults.
2. Primary disease is idiopathic (this is the most common etiology). The secondary form is due to infection (hepatitis C virus, hepatitis B virus, syphilis, malaria), drugs (gold, captopril, penicillamine), neoplasm, or lupus.
3. Prognosis is fair to good and course is variable; remission is common (in 40% of cases), but renal failure develops in 33% of patients. Steroids do not change survival rate.

CLINICAL PEARL 7-7

Glomerular Disease (GD) Versus Tubular Disease (TD)

1. TD is usually acute, whereas GD is more chronic.
2. TD is often caused by toxins (NSAIDs, contrast, myoglobin, drugs); GD is typically not caused by toxins.
3. TD does not cause nephrotic syndrome, GD does.
4. TD does not need biopsy, GD often does.
5. Steroids used for GD, not TD.
6. Immunosuppressive medications used for GD, not TD.

D. IgA Nephropathy

1. Asymptomatic recurrent hematuria/mild proteinuria is common. **This is the most common cause of glomerular hematuria.** Gross hematuria **1 to 3 days** after an upper respiratory infection (or other viral infection or exercise) is common (as opposed to weeks after a URI in PSGN).
2. Renal function is usually normal.
3. Mesangial deposition of IgA and C3 are seen on electron microscopy.
4. The prognosis in most patients is good with preservation of renal function (renal insufficiency may develop in 25%).
5. Some advocate steroids for unstable disease, but no therapy has been proven to be effective.

E. Hereditary Nephritis (Alport Syndrome)

1. X-linked or autosomal dominant inheritance with variable penetrance
2. Features include hematuria, pyuria, proteinuria, high-frequency hearing loss without deafness, progressive renal failure
3. No effective treatment

Secondary Glomerular Disorders

A. Diabetic Nephropathy—most common cause of ESRD (see Chapter 4)

B. Hypertensive Nephropathy—see Renal Vascular Disease section

C. Lupus—see Chapter 6

D. Membranoproliferative GN

1. Can present with proteinuria/nephrotic syndrome or hematuria/nephritis
2. Usually due to hepatitis C infection; other causes include hepatitis B, syphilis, and lupus
3. Common association with cryoglobulinemia

4. The prognosis is poor. Renal failure develops in 50% of patients. Treatment is rarely effective

E. Poststreptococcal GN—most common cause of nephritic syndrome

1. Occurs after infection with group A β-hemolytic streptococcal infection of the upper respiratory tract (or skin—impetigo). The GN develops about 10 to 14 days after infection. Primarily affects children (ages 2 to 6 years).
2. Features include **hematuria,** edema, HTN, low complement levels, and proteinuria.
3. Antistreptolysin-O may be elevated.
4. It is self-limited (usually resolves in weeks to months) with an excellent prognosis. Some cases develop into rapidly progressive GN (more commonly in adults).
5. Therapy is primarily supportive: antihypertensives, loop diuretics for edema; the use of antibiotics is controversial but has not been shown to prevent disease when given during acute streptococcal infection. Steroids may be helpful in severe cases.

F. Anti-GBM Disease (Goodpasture Syndrome)

1. Classic triad of proliferative GN (usually crescentic), pulmonary hemorrhage, and IgG antiglomerular basement membrane antibody.
2. Clinical features: rapidly progressive renal failure, hemoptysis, cough, and dyspnea
3. Lung disease precedes kidney disease by days to weeks.
4. Renal biopsy shows linear immunofluorescence pattern.
5. Treat with plasmapheresis to remove circulating anti-IgG antibodies. Cyclophosphamide and steroids can decrease the formation of new antibodies.

G. Dysproteinemias—amyloidosis, light chain/heavy chain diseases

H. Sickle Cell Nephropathy—see Renal Vascular Disease section

I. HIV Nephropathy

1. Characteristics include proteinuria, edema, and hematuria.
2. Histopathology most often resembles a collapsing form of FSGS.
3. Treat with prednisone, ACE inhibitors, and antiretroviral therapy.

J. Granulomatosis With Polyangiitis—see Chapter 6.

K. PAN—see Chapter 6.

Tubulointerstitial Diseases

Acute Interstitial Nephritis

A. General Characteristics

1. Inflammation involving interstitium (tissue that surrounds glomeruli and tubules)
2. Accounts for 10% to 15% of cases of AKI
3. Causes
   a. **Acute allergic reaction to medication is the most common cause**—for example, penicillins, cephalosporins, sulfa drugs, diuretics (furosemide, thiazide), anticoagulants, phenytoin, rifampin, allopurinol, proton pump inhibitors.
   b. Infection (especially in children)—due to a variety of agents, including *Streptococcus* spp. and *Legionella pneumophila.*
   c. Collagen vascular diseases—for example, sarcoidosis.
   d. Autoimmune diseases—for example, SLE, Sjögren syndrome.

Quick HIT

Diagnosing AIN

In the setting of recent infection and/or start of a new medication, look for allergic symptoms (rash, fever, general aches/pains) and signs/symptoms of AKI.

Quick HIT

The diagnosis of AIN can be made if the patient is known to have been exposed to one of the offending agents, and has the following: rash, fever, acute renal insufficiency, and eosinophilia.

B. Clinical Features

1. Acute interstitial nephritis (AIN) causes intrinsic AKI and its associated symptoms.
2. Rash, fever, and eosinophilia are the classical findings.
3. Pyuria and hematuria may be present.

Quick HIT

Acute Versus Chronic Interstitial Nephritis

- **Acute** interstitial nephritis causes a rapid deterioration in renal function and is associated with interstitial eosinophils or lymphocytes.
- **Chronic** interstitial nephritis has a more indolent course and is associated with tubulointerstitial fibrosis and atrophy.

C. Diagnosis

1. Renal function tests (increased BUN and Cr levels)
2. Urinalysis
   a. **Eosinophils in the urine suggest the diagnosis, given the proper history and findings. However, this is not very sensitive and should not be tested without the presence of pyuria.**
   b. WBC and white cell casts are often seen.
   c. Mild proteinuria or microscopic hematuria may be present.

3. Note that it is often impossible to distinguish AIN from ATN based on clinical grounds alone. Renal biopsy is the only way to distinguish between the two, but is usually not performed given its invasiveness.

D. Treatment

1. Removing the offending agent is usually enough to reverse the clinical findings. If creatinine continues to increase after stopping the offending agent, steroids may help.
2. Treat infection if present.

Quick HIT

Analgesic Nephropathy Pearls

- Analgesic nephropathy is a form of toxic injury to the kidney due to excessive use of over-the-counter analgesics (those that contain phenacetin, acetaminophen, NSAIDs, or aspirin).
- It can manifest as interstitial nephritis (acute or chronic) or renal papillary necrosis.
- It may lead to acute or chronic renal failure.

Renal Papillary Necrosis

- Most commonly associated with analgesic nephropathy, diabetic nephropathy, sickle cell disease, urinary tract obstruction, UTI, chronic alcoholism, and renal transplant rejection. (A common mnemonic is POSTCARDS—Pyelonephritis, Obstruction, Sickle cell disease, Tuberculosis, Cirrhosis, Analgesics, Renal vein thrombosis, Diabetes, Systemic vasculitis)
- Diagnosis is typically made by excretory urogram—note change in papilla or medulla.
- Variable course: some patients have rapid progression, and others have a more indolent, chronic course.
- Sloughed, necrotic papillae can cause ureteral obstruction (presents with flank pain and hematuria).
- Treat the underlying cause, and stop the offending agents (e.g., NSAIDs).

TABLE 7-7 Renal Tubular Acidosis (RTA)

Type	Distinguishing Characteristics
1 (distal)	• Inability to secrete H^+ • Urine pH >6 • Nephrolithiasis and nephrocalcinosis **do** occur
2 (proximal)	• **Inability to reabsorb HCO_3^-** • **Increased bicarbonate excretion** • Nephrolithiasis and nephrocalcinosis do **not** occur
3 (mixed)	• Rare autosomal recessive disorder: carbonic anhydrase II deficiency • Characteristics of type I and II
4 (hyperaldosteronism)	• Decreased Na+ absorption and H^+ and K^+ secretion in distal tubule • Results in **hyperkalemia** and **acidic urine** • Nephrolithiasis and nephrocalcinosis are **rare**

Renal Tubular Acidosis

A. General Characteristics

1. Renal tubular acidosis (RTA) is a disorder of the renal tubules that leads to a nonanion gap metabolic acidosis (through different mechanisms detailed below). Glomerular function is normal (see Table 7-7).
2. It is characterized by a decrease in the H+ excreted in the urine, leading to acidemia and urine alkalosis.
3. There are three types of RTA (types 1, 2, and 4). (Type 3 RTA is a term that is no longer used.)

B. Type 1 (Distal)

1. The defect is an inability to secrete H+ at the distal tubule (thus bicarbonate cannot be dissociated from protons and recycled to further buffer the blood). This inability to acidify the urine and generate new bicarbonate results in metabolic acidosis. Although normally the urine pH can be as low as 4.7, in distal RTA the urine pH cannot be lowered below 6, regardless of the severity of metabolic acidosis.

2. It leads to increased excretion of ions (sodium, calcium, potassium, sulfate, phosphate), with the following effects:
   a. Decrease in ECF volume
   b. **Hypokalemia** (defect in H+/K+ pump in alpha-intercalated cell)
   c. **Renal stones/nephrocalcinosis** (due to increased calcium and phosphate excretion into alkaline urine)
   d. Rickets/osteomalacia in children
3. Leads to hypokalemic, hyperchloremic, nonanion gap metabolic acidosis
4. Symptoms are secondary to nephrolithiasis and nephrocalcinosis. Up to 70% of patients have kidney stones
5. Causes: congenital, multiple myeloma, nephrocalcinosis, nephrotoxicity (e.g., amphotericin B toxicity), autoimmune diseases (lupus, Sjögren syndrome), medullary sponge kidney, and analgesic nephropathy
6. Treatment
   a. Correct acidosis with sodium bicarbonate. This can also help prevent kidney stones, which is a major goal of therapy.
   b. Administer phosphate salts (promotes excretion of titratable acid).

C. Type 2 (Proximal)

1. The defect is an inability to reabsorb HCO_3^- at the proximal tubule, resulting in **increased excretion of bicarbonate in the urine** and metabolic acidosis. The patient also loses K+ and Na+ in the urine.
2. Characterized by hypokalemic, hyperchloremic nonanion gap metabolic acidosis (as in type 1 RTA)
3. Causes
   a. Fanconi syndrome (in children), defined as a generalized proximal resorption defect
   b. Cystinosis, Wilson disease, lead toxicity, multiple myeloma (monoclonal gammopathies are the major cause in adults), nephrotic syndrome, amyloidosis, acetazolamide
   c. The excretion of monoclonal light chains is a common feature, so multiple myeloma should always be ruled out in a patient with proximal RTA

4. Nephrolithiasis and nephrocalcinosis do not occur (as they do in type 1 RTA).
5. Treatment: treat the underlying cause
   a. Do not give bicarbonate to correct the acidosis because it will be excreted in the urine.
   b. Sodium restriction increases sodium reabsorption (and thus bicarbonate reabsorption) in the proximal tubule.

D. Type 4

1. This is the name for the normal anion gap metabolic acidosis that results from any condition that is associated with hypoaldosteronism, or increased renal resistance to aldosterone.
2. It is common in patients with interstitial renal disease and diabetic nephropathy.
3. It is characterized by decreased Na+ absorption and decreased H+ and K+ secretion in the distal tubule.
4. Unlike other types of RTA, **type 4 results in hyperkalemia** and acidic urine (although a nonanion gap metabolic acidosis still occurs).
5. Nephrolithiasis and nephrocalcinosis are rare.

Fanconi Syndrome

- Fanconi syndrome is a hereditary or acquired proximal tubule dysfunction that leads to defective transport of some of the following: glucose, amino acids, sodium, potassium, phosphate, uric acid, and bicarbonate. Recall that the proximal tubule is the primary site of resorption in the nephron.
- It is associated with glucosuria, phosphaturia (leads to skeletal problems: rickets/impaired growth in children; osteomalacia, osteoporosis, and pathologic fractures in adults), proteinuria, polyuria, dehydration, type 2 RTA, hypercalciuria, and hypokalemia.
- Treat with phosphate, potassium, alkali and salt supplementation, as well as adequate hydration.

Renal Cystic Diseases

Autosomal Dominant Polycystic Kidney Disease

A. General Characteristics

1. Polycystic kidney disease may be inherited as an autosomal dominant or autosomal recessive trait. Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of CKD (Figure 7-5).
2. The course is variable, but ESRD commonly develops in 50% of the patients (by late 50s or 60s); remainder have a normal lifespan. Renal failure occurs from cysts replacing renal parenchyma over time, as well as recurrent episodes of pyelonephritis and nephrolithiasis.

B. Clinical Features

1. Hematuria: usually visible and thought to be due to rupture of cysts into the collecting system
2. Abdominal pain: sources include pyelonephritis, stones, and hemorrhaging into cysts
3. HTN (in >50% of the cases)
4. Palpable kidneys on abdominal examination
5. Complications/associated findings
   a. Intracerebral berry aneurysm (in 5% to 20% of cases)—most do not rupture
   b. Infection of renal cysts; bleeding into cysts
   c. Renal failure (late in the disease)
   d. Kidney stones
   e. Heart valve abnormalities (especially mitral valve prolapse)
   f. Cysts in other organs (liver, spleen, pancreas, brain)
   g. Diverticula (colon)
   h. Hernias (abdominal/inguinal)

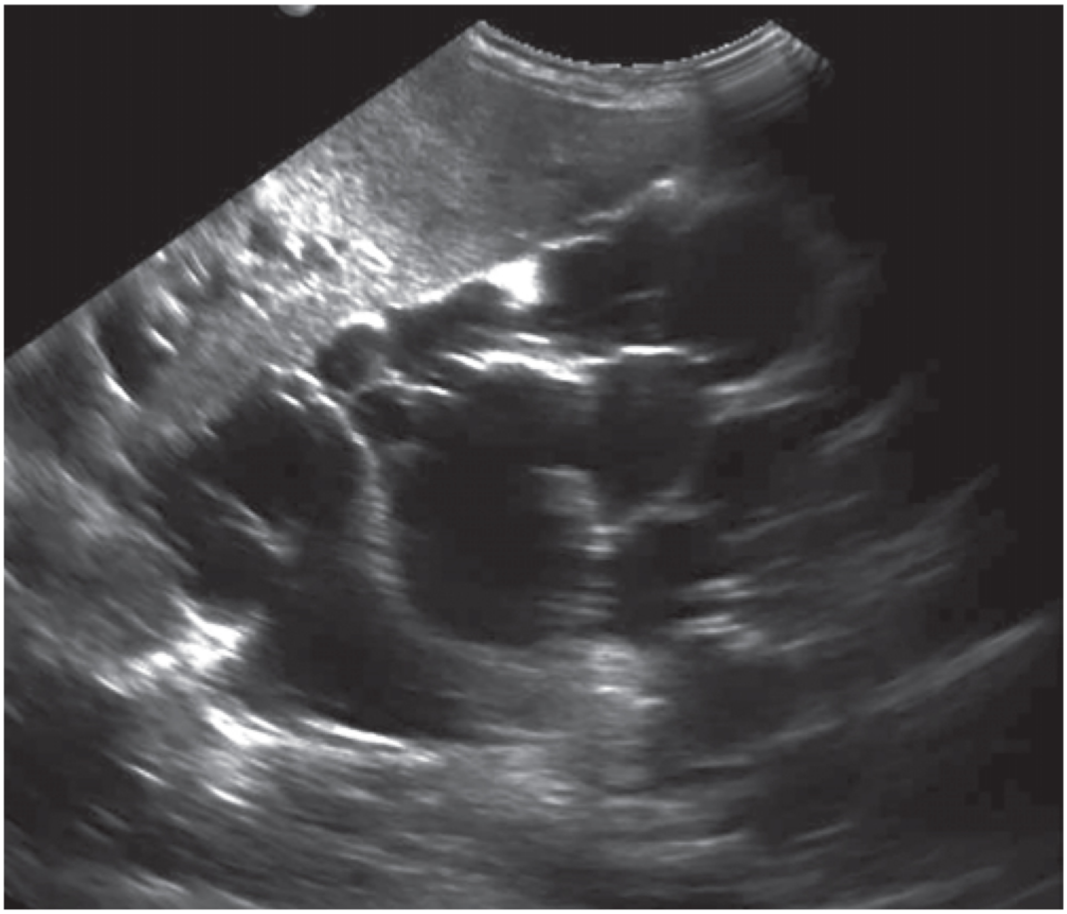


FIGURE 7-5 The renal ultrasound demonstrates polycystic kidney disease.
(Reprinted with permission from Kawamura DM, Nolan TD. *Diagnostic Medical Sonography: Abdomen and Superficial Structures*. 4th ed. Wolters Kluwer; 2018. Figure 5-23F.)

***Quick* HIT**

ADPKD presents with:
- Pain
- Hematuria
- Infection
- Hypertension
- Kidney stones

C. Diagnosis

1. Ultrasound, CT, or MRI will show multiple cysts.

D. Treatment

1. No curative therapy is available.
2. Treat infection with antibiotics.
3. Control HTN and other cardiovascular risk factors.

A 49-year-old man presents to his physician for a routine examination and is found to be hypertensive. He has no past medical history, and his family history is unknown since he was adopted. Blood work shows a BUN and creatinine of 21 mg/dL and 1.6 mg/dL, respectively. Abdominal ultrasound shows bilaterally enlarged kidneys with many cysts.

Which of the following is NOT a potential complication of this disease?

A. Hypertension
B. Renal cell carcinoma
C. Subarachnoid hemorrhage
D. Development of hepatic cysts
E. Aortic regurgitation

- **The answer is B: Renal cell carcinoma.** Autosomal dominant polycystic kidney disease (ADPKD) is caused by a mutation in the PKD1 (more common) or PKD2 genes and causes progressive renal disease starting most commonly in the fourth decade. There is usually a positive family history, so many patients are diagnosed early with a screening ultrasound (or other imaging modality) that shows multiple large cysts in both kidneys. **(D)** Hepatic and pancreatic cysts can also develop. **(A)** Any cause of renal failure will produce hypertension. Treatment with ACE inhibitors or ARBs, along with control of hypertension, can slow down the progression of the disease but there is no cure for the disease. **(C)** The most concerning extrarenal complication of ADPKD is cerebral aneurysms, which can rupture and cause intracerebral or subarachnoid hemorrhage. **(E)** Valvular disease is also very common in these patients, especially mitral valve prolapse and aortic regurgitation. **(B)** Pancreatic cysts may slightly increase the risk of certain types of pancreatic cancer, but ADPKD is not associated with an increased risk of renal cell carcinoma.

Autosomal Recessive Polycystic Kidney Disease

A. General Characteristics

1. Autosomal recessive polycystic kidney disease (ARPKD) was previously called infantile polycystic kidney disease. It is characterized by cysts predominantly in the renal collecting ducts as well as hepatic fibrosis.
2. It is less common compared to the ADPKD, though the true incidence is unknown since many affected newborns die without proper diagnosis.
3. As with ADPKD, there is a wide variability in the level of renal impairment. However, most patients ultimately will experience progressive renal failure.

B. Clinical Features

1. Liver involvement is always present, and may be the dominant clinical feature, especially in older individuals
   a. Hepatic complications include portal HTN and cholangitis
2. Kidneys are increased in size which may cause severe abdominal distension
3. HTN
4. Pulmonary insufficiency secondary to pulmonary hypoplasia and enlarged kidneys limiting diaphragmatic movement may be severe. Pulmonary complications are the leading cause of morbidity and mortality in the neonatal period
5. Newborns with severe ARPKD may present with Potter syndrome, which is the constellation of clinical features associated with decreased amniotic fluid (oligohydramnios). Potter syndrome is characterized by hypoplasia of the lungs, limb abnormalities (e.g., club feet), and characteristic abnormal facies

C. Diagnosis

1. Some cases are detected prenatally due to the widespread use of ultrasound during pregnancy. Less severe cases may not be detected

until much later.
2. Oligohydramnios during pregnancy usually indicates severe disease.
3. Ultrasound will show characteristic renal cysts in the absence of renal cysts in either parent. Ultrasound will also show hepatomegaly and dilated bile ducts.
4. Molecular genetic testing may confirm the disease in cases where the diagnosis is unclear.

D. Treatment

1. No curative therapy is available.
2. Manage respiratory issues in newborns, and treat ESRD with renal replacement therapy.

Medullary Sponge Kidney

- Characterized by cystic dilation of the collecting ducts (Figure 7-6)
- May present with hematuria, UTIs, or nephrolithiasis, can often also be asymptomatic
- Thought to be associated with hyperparathyroidism and parathyroid adenoma
- Diagnosed by IVP
- No treatment is necessary other than the prevention of stone formation and the treatment of recurrent UTIs

Simple Renal Cysts

- Very common (50% of the people over age 50); incidence increases with age
- May be single or multiple; usually asymptomatic and discovered incidentally on abdominal ultrasound or other imaging study
- Occasionally associated with hematuria or pain from rupture, infection, or hypertension
- No treatment is necessary in most cases

FIGURE 7-6 **Excretory urogram in a patient with medullary sponge kidney, showing multiple spherical or oval dilatations of medullary collecting ducts in all papillary groups of the right kidney, giving a "bouquets of flowers" appearance.**
(Reprinted with permission from Schrier RW. *Diseases of the Kidney and Urinary Tract*. 8th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2007. Figure 17-8.)

Renal Vascular Disease

Renal Artery Stenosis (Renovascular Hypertension)

A. General Characteristics

1. Renal artery stenosis causes a decrease in blood flow to the juxtaglomerular apparatus. As a result, the renin–angiotensin–aldosterone system becomes activated, leading to HTN.
2. **This is the most common cause of secondary HTN.**

B. Causes

1. Atherosclerosis
   a. Accounts for two-thirds of the cases (most often in elderly men)
   b. Bilateral in up to one-third of the cases
   c. Smoking and high cholesterol levels are predisposing factors.
2. Fibromuscular dysplasia
   a. Usually seen in young females
   b. Bilateral in 50% of patients

C. Clinical Features

1. HTN—look for a sudden onset of HTN in a patient without a family history, that is severe (may cause malignant HTN), and/or that is refractory to multiple antihypertensive agents
2. Decreased renal function
3. Abdominal bruit (RUQ, LUQ, or epigastrium) is present in 50% to 80% of patients; it is especially common in patients with fibromuscular hyperplasia

Quick HIT

ACE inhibitors should be used carefully in patients with renovascular HTN.

Quick HIT

Suspect renovascular HTN in the following situations:

- Malignant HTN
- Sudden onset of HTN
- HTN that suddenly worsens
- HTN that does not respond to standard medical therapy

D. Diagnosis

1. Renal arteriogram is the gold standard, but is invasive.
2. Duplex Doppler ultrasound, CT angiography, and MR angiography are all alternative options for initial testing.

A 52-year-old man presents for a routine physical examination. He has not been to a primary care physician since he was a teenager, and now he wants a colonoscopy since his friend was recently diagnosed with colon cancer. He denies any medical history and takes no medications. He is found to be hypertensive during his clinic appointment (164/98 mmHg), and the diagnosis of hypertension is later confirmed with the use of outpatient blood pressure monitoring. On examination, a bruit is heard over the left carotid artery, an S4 is heard on cardiac auscultation, and he has weak lower-extremity pulses. He has baseline laboratory tests drawn, is started on lisinopril, and is instructed to follow up for repeat laboratory work 1 week later. At the follow-up appointment, his blood pressure is 172/102 mmHg and the following laboratory results are seen.

	First Visit	**Second Visit**
Sodium	142 mEq/L	137 mEq/L
Potassium	3.2 mEq/L	4.3 mEq/L
Chloride	105 mEq/L	103 mEq/L
Bicarbonate	27 mEq/L	23 mEq/L
Blood urea nitrogen	14 mg/dL	24 mEq/L
Creatinine	1.1 mg/dL	1.8 mg/dL
Glucose	154 mg/dL (nonfasting)	120 mg/dL (fasting)

What should be done next in the management of this patient?

A. Add hydrochlorothiazide

B. Add metformin
C. Stop lisinopril
D. Continue the current management and repeat laboratory tests in 2 weeks

- **The answer is C: Stop lisinopril.** This patient has an abrupt rise in creatinine after 1 week of taking an ACE inhibitor, indicating that this medication may have caused acute renal failure. One potential side effect of ACE inhibitors and ARBs is a reduction in GFR, which occurs within several days after starting therapy. Although it is rare for these medications to cause AKI, patients with the following conditions are at risk: chronic kidney disease (CKD), polycystic kidney disease, heart failure, hypertensive nephrosclerosis, and bilateral renal artery stenosis. This patient has hypertension with physical examination findings that suggest chronic hypertension (S4) and peripheral arterial disease (carotid bruit, weak peripheral pulses). In addition, he has hypokalemia at baseline. One condition that should be considered is bilateral renal artery stenosis from atherosclerosis. Because patients with this condition have poor kidney perfusion at baseline, they are in a high renin, high aldosterone state (potentially causing hypokalemia) with dilation of the afferent arteriole and vasoconstriction of the efferent arteriole to maintain GFR. ACE inhibitors cause relaxation of the efferent arteriole through a reduction in angiotensin II, further decreasing GFR and potentially causing ischemic AKI. Other clues to the diagnosis of renal artery stenosis are a renal bruit on examination and episodes of flash pulmonary edema. Bilateral renal artery stenosis can also be caused by fibromuscular dysplasia, which is less common and typically occurs in young women. **(A)** The first step in the treatment of AKI is to remove the offending agent, so treating his hypertension and ignoring his AKI is not the right answer. **(B)** The patient is prediabetic and should be encouraged to change his diet and lifestyle before pursuing pharmacotherapy. **(D)** It is not appropriate to continue therapy with an agent that precipitated AKI.

E. Treatment

1. Revascularization with percutaneous transluminal renal angioplasty (PRTA) is the initial treatment in most patients; it has a higher success rate and a lower restenosis rate with fibromuscular dysplasia than with the atherosclerotic type.
2. Surgery if PRTA is not successful (bypass).
3. Conservative medical therapy (ACE inhibitors, calcium channel blockers) may be tried alone or in combination with revascularization procedures. ACE inhibitors may inhibit kidneys' natural mechanism to increase GFR when RBF is low from stenosis (efferent arteriole constriction) and thus should be used carefully.

Renal Vein Thrombosis

- May be seen in the following clinical settings: nephrotic syndrome (due to increased risk of VTE), invasion of renal vein by renal cell carcinoma (RCC), trauma, pregnancy/oral contraceptives, extrinsic compression (retroperitoneal fibrosis, aortic aneurysm, lymphadenopathy), or severe dehydration (in infants)
- Clinical features depend on the acuity and severity of the process and include decreased renal perfusion (can lead to renal failure), flank pain, HTN, hematuria, and proteinuria. Chronic thromboses are largely asymptomatic but may lead to progressive renal damage or PE
- Diagnostic tests include selective renal venography visualizing the occluding thrombus (definitive study) or IVP
- Anticoagulation

Atheroembolic Disease of the Renal Arteries

- Refers to showers of cholesterol crystals that dislodge from plaques in large arteries and embolize to the renal vasculature.
- Can occur in other organs as well, such as the retina, brain, or skin.
- Refer to cholesterol embolization syndrome in Chapter 1.

Quick HIT

Nephrosclerosis due to HTN is the second most common cause of ESRD (diabetes is the most common cause).

Hypertensive Nephrosclerosis

A. Definition

Systemic HTN increases capillary hydrostatic pressure in the glomeruli, leading to benign or malignant sclerosis.

1. Benign nephrosclerosis—hypertrophic thickening of the glomerular afferent arterioles and glomeruli themselves (global or focal segmental) develops in patients with long-standing HTN.
   a. Results in mild to moderate increase in Cr levels, microscopic hematuria, and mild proteinuria.
   b. Advanced disease can lead to ESRD.
2. Malignant nephrosclerosis—this accelerated variant of nephrosclerosis typically may develop in a patient with malignant hypertension or with long-standing benign HTN.
   a. Characterized by a rapid decrease in renal function and accelerated HTN due to diffuse intrarenal vascular injury. It is also known as acute hypertensive nephrosclerosis.
   b. African American men are the most susceptible.
   c. Clinical manifestations include:
      - Markedly elevated BP (papilledema, cardiac decompensation, CNS findings).
      - Renal manifestations: a rapid increase in Cr, proteinuria, hematuria, RBC and WBC casts in urine sediment, and sometimes nephrotic syndrome.
      - Microangiopathic hemolytic anemia may also be present.

B. Treatment

1. The most important treatment for both benign and malignant forms is controlling the BP (see Chapter 12). It is not clear which blood pressure agents should be used in the chronic setting, or how effective

they are once frank albuminuria is present. Care must also be taken to avoid acutely dropping renal perfusion.

2. In advanced disease, treat as for CKD. Dialysis may be required.

Sickle Cell Nephropathy

- If ischemic injury to the renal tubules occurs (due to hemodynamic changes or nephrotoxins), there is increased risk of dehydration (from impaired urine concentration), precipitating sickling crises.
- This sickling of RBCs in the microvasculature leads to infarction. In the kidney this occurs mostly in the renal papilla. Sequelae of recurrent papillary infarction include papillary necrosis, ATN, and renal failure, as well as a high frequency of UTIs.
- Nephrotic syndrome can also develop (which can lead to renal failure).
- It progresses to ESRD in approximately 5% of the patients.
- ACE inhibitors may be helpful.

Stones and Obstructions

Nephrolithiasis

A. General Characteristics

1. Nephrolithiasis is the development of stones within the urinary tract
2. Sites of obstruction
   a. Ureterovesicular junction—most common site of impaction
   b. Calyx of the kidney
   c. Ureteropelvic junction
   d. Intersection of the ureter and the iliac vessels (near the pelvic brim)
3. Risk factors
   a. In general, precipitation is dependent on factors which affect the relative concentration of certain stone-forming substances within the urine as well as urine pH
   b. Low fluid intake—most common and preventable risk factor which can predispose to concentration of urine and precipitation of crystals

c. Family history
d. Conditions known to precipitate stone formation (e.g., gout [hyperuricemia], Crohn disease [hyperoxaluria], hyperparathyroidism [hypercalciuria], type 1 RTA [increased urine pH])
e. Medications (e.g., loop diuretics [hypercalciuria], acetazolamide [increased urine pH], antacids, chemotherapeutic drugs that cause cell breakdown [uric acid stones], medications which can themselves precipitate in the nephrons [acyclovir, sulfadiazine])
f. Male gender (three times more likely to have urolithiasis)
g. UTIs (especially with urease-producing bacteria leading to struvite stones)
h. Dietary factors—low calcium and high oxalate intake, both of which lead to hyperoxaluria (high calcium intake itself is rarely associated with increased stones)

***Quick* HIT**

Causes of Hypercalciuria and Hyperoxaluria

Causes of hypercalciuria

- ↑ Intestinal absorption of calcium, not usually from diet alone
- ↓ Renal reabsorption of calcium, leading to ↑ renal excretion of calcium
- ↑ Bone reabsorption of calcium
- Primary hyperparathyroidism
- Sarcoidosis
- Malignancy
- Vitamin D excess
- Acidemia, leading to displacement of calcium from albumin

Causes of hyperoxaluria

- Severe steatorrhea of any cause can lead to calcium oxalate stones (due to calcium binding to fat instead of oxalate in intestine and thus ↑ absorption of free oxalate)
- Small bowel disease, Crohn disease
- Pyridoxine deficiency
- Vitamin C excess
- Ethylene glycol ingestion

4. Types of stones
   a. Calcium stones (most common form)

- **Account for 80% to 85% of urinary stones;** composed of calcium oxalate or calcium phosphate (less often) or both
- Bipyramidal or biconcave ovals
- Radiodense (i.e., visible on an abdominal radiograph)
- Secondary to hypercalciuria and hyperoxaluria, which can be due to a variety of causes
- Acidic urine pH promotes calcium oxalate stone formation while a basic pH induces calcium phosphate stones

b. Uric acid stones (second most common)
- Account for 10% of stones
- Flat square plates
- **Stones are radiolucent (cannot be seen on an abdominal radiograph)**—require CT, ultrasound, or IVP for detection
- These are associated with hyperuricemia, secondary to gout or to chemotherapeutic treatment of leukemias and lymphomas with high cell destruction. The release of purines from dying cells leads to hyperuricemia
- A persistently acidic urine pH (<5.5) promotes uric acid stone formation

c. Struvite stones (staghorn stones)
- Account for 5% to 10% of stones
- Radiodense (visible on an abdominal radiograph); rectangular prisms
- Occur in patients with recurrent UTIs due to urease-producing organisms (*Proteus, Klebsiella, Serratia, Enterobacter* spp.)
- They are facilitated by alkaline urine: urea-splitting bacteria convert urea to ammonia, thus producing the alkaline urine
- The resultant ammonia combines with magnesium and phosphate to form struvite calculi, which may involve the entire renal collecting system

d. Cystine stones
- Account for 1% of urinary stones
- Genetic predisposition—cystinuria (autosomal recessive), usually seen in children
- Hexagon-shaped crystals are poorly visualized

5. Clinical course

a. If a stone is >1 cm, it is unlikely to pass spontaneously. **Stones <0.5 cm usually do pass spontaneously**
b. Recurrence is common. Up to 50% of the patients have recurrences within 10 years of having the first stone

Quick HIT

Classic Presentation of Nephrolithiasis

- Sudden onset of colicky flank pain that radiates into groin
- Urinalysis showing hematuria

B. Clinical Features

1. Renal colic—refers to the pain associated with passing a kidney stone into the ureter, with ureteral obstruction and spasm
   a. Description of pain—begins suddenly and soon may become severe (patient cannot sit still—usually writhes in excruciating pain). Pain may occur in waves or paroxysms.
   b. Location of pain—begins in the flank and radiates anteriorly toward the groin (i.e., follows path of the stone)
2. Nausea and vomiting are common
3. Hematuria (in over 90% of the cases)
4. UTI

C. Diagnosis

1. Laboratory testing
   a. Urinalysis
      - Reveals either microscopic or gross hematuria
      - Evaluates for UTI
      - Examine the urinary sediment for crystals (calcium, cystine, uric acid, or struvite crystals)
      - Determine the urinary pH—alkaline urine might indicate the presence of urease-producing bacteria that cause an infection stone. Acidic urine is suggestive of uric acid stones
   b. Urine culture—obtain if infection is suspected

c. Twenty-four–hour urine—collect to assess Cr, calcium, uric acid, oxalate, and citrate levels. Usually done for patients with recurrent stones to assess risk factors and etiology
d. Serum chemistry—obtain BUN and Cr levels (for evaluation of renal function, if kidney parenchyma are not damaged this will likely be normal) and also calcium, uric acid, and phosphate levels
e. Stone analysis: patient can strain urine for stones, which can then be sent for analysis of chemical composition

2. Imaging
   a. Used to diagnose a stone and evaluate for obstruction (hydronephrosis)
   b. CT scan without contrast is typically the imaging study of choice, though ultrasound of the kidneys and bladder can also be used

Quick HIT

Having the stone for analysis is very helpful both in treatment and in preventing recurrence. Likewise, reporting a history of stones and their composition (if determined) is very helpful. The patient should attempt to recover the stone that is passed (strain urine).

D. Treatment

1. General measures (for all types of stones)
   a. Analgesic medications (e.g., ketorolac, opioids if needed)
   b. IV fluids
   c. Alpha-1 blockers (tamsulosin) may be used to facilitate stone passage.
   d. Antibiotics—if UTI is present
   e. Outpatient management is appropriate for most patients. Indications for hospital admission include:
      - Pain not controlled with oral medications
      - Anuria (usually in patients with one kidney)
      - Renal colic plus UTI and/or fever
      - Large stone (>1 cm) that is unlikely to pass spontaneously
2. Specific measures (based on severity of pain)

a. Surgical intervention is necessary in cases of ongoing obstruction and persistent pain not controlled by narcotics, signs of infection/sepsis, kidney injury/failure, or failure to respond to conservative measures.
   - Extracorporeal shock wave lithotripsy (most common method) breaks the stone apart using sound waves; once the calculus is fragmented, the stone can pass spontaneously. Best for stones that are >5 mm but <2 cm in diameter.

3. Other options include ureteroscopy with laser lithotripsy, percutaneous nephrolithotomy, or laparoscopic stone removal as a last resort.
4. Prevention of recurrence
   a. Dietary measures
   - High fluid intake is essential (keep urine volume at 2 L/day)
   - Limit animal protein intake in patients with hyperuricosuria (uric acid stones).
   - Advise patient to not to restrict calcium in their diet as lower intake is associated with hyperoxaluria and increased stones (unless in rare cases when dietary intake is identified as likely etiology of stones).

   b. Pharmacologic measures
   - Thiazide diuretics reduce urinary calcium and have been found to lower recurrence rates, especially in patients with hypercalciuria.
   - Allopurinol is effective in preventing recurrence in patients with high uric acid levels in the urine.

Urinary Tract Obstruction

A. General Characteristics

1. Can lead to renal insufficiency and hydronephrosis (dilation of urinary tract, specifically the pelvis and calyces)
2. More common in men (due to BPH and prostate cancer)
3. Urinary tract obstruction does not usually cause AKI unless the obstruction is bilateral or there is pre-existing renal damage
4. Classification
   a. Acute versus chronic obstruction
   - Acute obstruction—clinical features are sudden in onset

- Chronic obstruction—this causes progressive renal failure/uremia, recurrent infections, and bladder calculi

b. Lower versus upper tract obstruction
   - Lower tract obstruction (below ureterovesical junction)—affects urination
   - Upper tract obstruction (above ureterovesical junction)—typically causes renal colic

c. Complete versus partial obstruction

d. Unilateral versus bilateral obstruction (if upper tract)

5. Degree of damage to kidneys and likelihood of return to normal renal function is dependent on the severity and duration of the obstruction.
6. Causes

   a. Lower tract obstruction
   - BPH, prostate cancer
   - Urethral stricture, stone
   - Neurogenic bladder (multiple sclerosis, diabetes)
   - Trauma (pelvic fracture or straddle injury)
   - Bladder cancer

   b. Upper tract obstruction
   - Intrinsic causes—kidney stones, blood clots, sloughed papilla (RPN), crystal deposition (e.g., uric acid), tumors, strictures, ureteropelvic or ureterovesical junction dysfunction
   - Extrinsic causes—pregnancy, tumors (gynecologic, metastatic), abdominal aortic aneurysm, retroperitoneal fibrosis, endometriosis, prolapse, hematomas, Crohn disease, diverticulitis

Quick HIT

Evaluation of Urinary Tract Obstruction
- History: Duration of symptoms, UTIs, history of nephrolithiasis, history of surgery
- Physical: Suprapubic mass (distended bladder), flank mass (hydronephrosis)
- Features of CKD

B. Clinical Features (depend on duration, location, cause, and duration of obstruction)

1. Renal colic and pain—this is more common with acute obstruction (kidney stones, sloughed papilla, blood clot); pain may manifest only during urination. Chronic obstruction may be asymptomatic
2. Suprapubic pain and distention—may be seen in lower urinary tract obstruction
3. Urine output may be normal, though oliguria/anuria may be seen in complete obstruction (usually in lower tract obstruction)
4. Signs/symptoms of UTI, which can be a result of urinary stasis or stones
5. Hypertension, particular in oliguric patients due to sodium/fluid retention
6. Renal failure

Quick HIT

If a patient has an acute obstruction **and** a UTI, emergent diagnostic tests (renal ultrasound or excretory urogram) are indicated. Intervene immediately to relieve the obstruction.

Quick HIT

Patients can have urinary tract obstruction without hydronephrosis on imaging, and patients can also have hydronephrosis on imaging without urinary tract obstruction.

C. Diagnosis

1. **Renal ultrasound is the preferred diagnostic test**. It is very sensitive and specific for identifying hydronephrosis.
2. If urinary retention from bladder obstruction (e.g., BPH) is suspected, then bladder ultrasound and catheterization can provide immediate relief and is diagnostic.
3. Urinalysis (may reveal hematuria or proteinuria), standard laboratory tests (e.g., CBC, electrolytes, BUN, Cr).

4. If nephrolithiasis suspected, ultrasound or CT should be done to confirm the diagnosis.
5. Cystoscopy with retrograde pyelography can be used in patients where suspicion remains high but initial diagnostic studies are negative.

A 76-year-old man is hospitalized for pneumonia and was started on empiric antibiotics. He developed a rash in response to the antibiotics, and the symptoms were somewhat relieved with diphenhydramine. Several days after this, the patient developed oliguria. His laboratory values are shown below.

Sodium	138 mEq/L
Potassium	4.8 mEq/L
Chloride	108 mEq/L
Bicarbonate	20 mEq/L
Blood urea nitrogen	18 mg/dL
Creatinine	1.6 mg/dL (baseline 1.1 mg/dL)
Glucose	114 mg/dL

A urinalysis is unremarkable. A renal ultrasound shows bilateral dilation of the renal pelvis and calyces.

Which of the following is the most likely anatomic site of obstruction in this patient?

A. Renal arteries
B. Ureters
C. Renal tubules
D. Bladder
E. Renal veins
F. Ureteropelvic junction

- **The answer is D: Bladder.** The abrupt onset of oliguria with a rise in creatinine indicates AKI, and the renal ultrasound showing hydronephrosis narrows the differential diagnosis to most likely be a postrenal AKI (obstructive nephropathy). An important historical clue given in the vignette is the administration of diphenhydramine, which is an antihistamine that also has anticholinergic properties. Patients with BPH, which is a common diagnosis in older men, may

also experience postrenal AKI with anticholinergics. This patient should have a urethral or suprapubic catheter placed to decompress the bladder and urinary tract. **(A, C, E)** An obstruction in the renal arteries, tubules, or veins would cause renal injury but would not cause an obstruction in the urinary tract leading to hydronephrosis. **(B, F)** The ureters and ureteropelvic junction are common places for kidney stones to become lodged; however, it is important to know that AKI from ureteral obstruction occurs only if the obstruction is bilateral. This is due to the fact that obstruction of one ureter decreases the filtration rate of that kidney, but the other kidney will increase its GFR to compensate.

D. Treatment

1. Treatment depends on duration, severity, location, and cause of the obstruction.
2. Location of obstruction
   a. Lower urinary tract obstruction
      - Urinary catheter—for acute obstruction (can be diagnostic and therapeutic), urethral catheter is first choice but if passage is difficult or contraindicated, suprapubic catheter may be used
      - Dilatation or internal urethrotomy—if cause is urethral strictures
      - Prostatectomy—if BPH is the cause

   b. Upper urinary tract obstruction
      - Nephrostomy tube drainage—for acute obstruction, particularly in urgent setting when kidney function is impaired or infection is present and source control is needed
      - Ureteral stent (through cystoscope)—if ureteral obstruction
3. Duration and severity of obstruction
   a. Acute complete obstruction—pain or renal failure may be present. This requires immediate therapy

   b. Acute partial obstruction—usually due to stones (see the Treatment section of Nephrolithiasis)

   c. Chronic partial obstruction—this requires immediate therapy only when infection, severe symptoms, renal failure, or urinary retention is present

Neoplasms

Prostate Cancer

A. General Characteristics

Prostate cancer is the second most common form of cancer in men worldwide (see also Clinical Pearl 7-8 and Figure 7-7). Ninety-five percent are adenocarcinomas which arise in the peripheral (outermost) zone of the prostate.

1. Risk factors
   a. Age (most important risk factor)
   b. African American race
   c. High-fat diet
   d. Positive family history
   e. Exposure to herbicides and pesticides—certain occupations, such as farming and work in industrial chemical industry, present a higher risk

B. Clinical Features

1. Early stages—it is most commonly asymptomatic. Cancer begins in the periphery of the gland and moves centrally. Thus, obstructive symptoms occur late. In fact, by the time prostate cancer causes urinary obstruction, it often has metastasized to bone or lymph nodes.
2. As the cancer grows locally—symptoms due to obstruction of the urethra occur as the other zones of the prostate are affected: difficulty in voiding, dysuria, and increased urinary frequency.
3. Advanced stages/metastasis—bone pain from metastases (most commonly vertebral bodies, pelvis, and long bones in legs), weight loss

CLINICAL PEARL 7-8

Prostate-Specific Antigen, Digital Rectal Examination, and Transrectal Ultrasonography

- If PSA level >10 ng/mL, TRUS with biopsy is indicated, regardless of DRE findings.
- If DRE is abnormal, TRUS with biopsy is indicated, regardless of PSA level.
- If PSA is <4.0 ng/mL and DRE is negative, annual follow-up is indicated.
- If PSA is 4.1 to 10.0 and DRE is negative, biopsy is usually recommended.

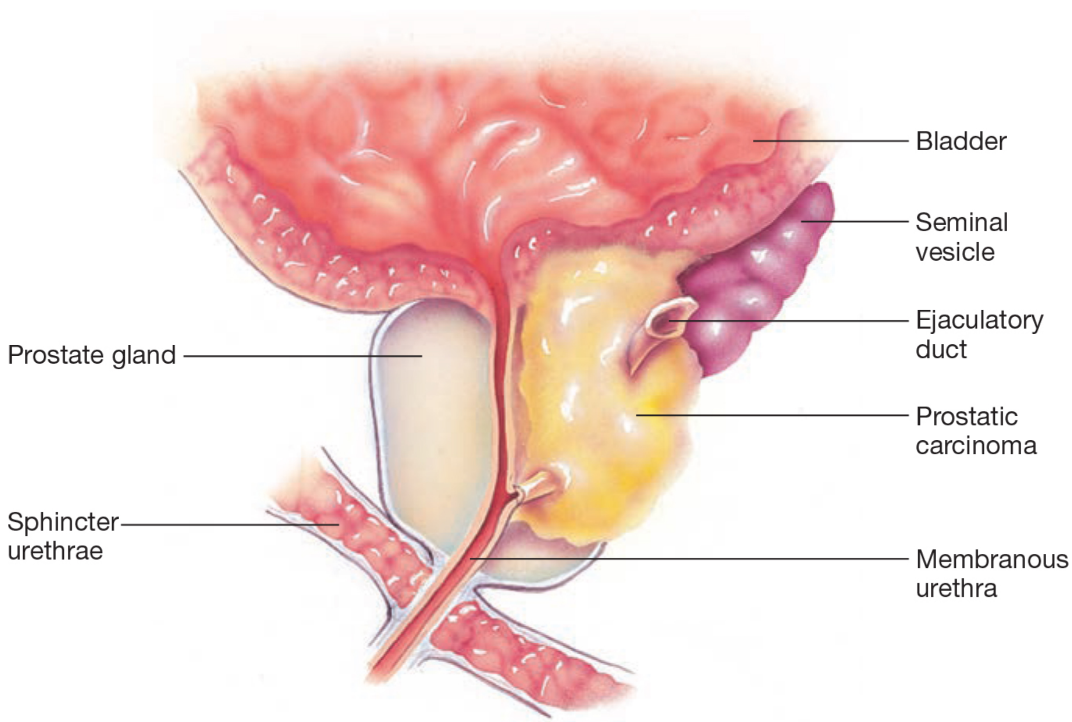


FIGURE 7-7 Prostate cancer.
(Asset provided by Anatomical Chart Co.)

Quick HIT

Vertebral metastasis may manifest itself as low back pain in an elderly man with prostate cancer.

C. Diagnosis

1. Digital rectal examination (DRE).
   a. Carcinoma is characteristically hard, nodular, and irregular.
   b. Normal prostate feels like a thenar eminence. Cancer feels like a knuckle. Men with induration, asymmetry, or palpable nodularity of prostate need a biopsy, especially if over age 45.
   c. If DRE is abnormal, transrectal ultrasonography (TRUS) with biopsy is indicated, regardless of the prostate-specific antigen (PSA) level.
   d. When palpable, 60% to 70% have spread beyond the prostate.
2. PSA
   a. Not used routinely as a screening test as the absolute risk reduction of death from prostate cancer is small (growth is very slow and most will die of other causes) and the harm from unnecessary biopsies and interventions may be more significant.
   b. PSA is not cancer specific. PSA levels also increase as a result of the following:
      - Prostatic massage (but DRE does not change PSA levels)
      - Needle biopsy
      - Cystoscopy
      - BPH
      - Prostatitis
      - Advanced age
   c. Refinements of the PSA assay—some strategies for improving the diagnostic capability of the PSA test include:
      - Age-adjusted PSA (because PSA normally increases with age).
      - PSA velocity—analysis of the rate of increase in the level with time.
      - Quantifying free and protein-bound forms of serum PSA—PSA produced by prostate cancer tends to be bound by plasma proteins, whereas PSA produced by normal cells is more likely to be free in plasma.
      - PSA density—correlation of PSA levels with prostate volume.

Quick HIT

The combination of DRE and PSA levels can detect up to 60% of prostate cancers while they are still localized.

Quick HIT

Key points about PSA:

1. The higher the PSA, the higher the cancer risk
2. Normal PSA does not rule out prostate cancer
3. Not used as a screening test
4. If patient requests the test, order it

3. TRUS with biopsy
   a. May need to repeat biopsies for definitive diagnosis
   b. Indications
      - PSA >10 ng/dL (or possibly lower). If PSA is >10, chance of finding cancer is over 50%.
      - PSA velocity >0.75 per year
      - Abnormal DRE
4. Other tests in the evaluation include a bone scan, plain radiographs of the pelvis and spine, and a CT scan of the pelvis to evaluate for metastatic disease.

Quick HIT

Stages of Prostate Cancer

- Stage A—nonpalpable, confined to prostate
- Stage B—palpable nodule, but confined to prostate
- Stage C—extends beyond capsule without metastasis
- Stage D—metastatic disease

D. Treatment

1. Localized disease (to prostate)—this is usually a curable disease. Treatment choice often depends on risk for progression and patient preference. Options include active surveillance, androgen deprivation

therapy, radiation therapy, brachytherapy, and radical prostatectomy. Most common complications of prostatectomy are erectile dysfunction and urinary incontinence.

2. If disease progression occurs while on androgen deprivation therapy, this is referred to as castration-resistant prostate cancer. Treatment options depend on whether disease is metastatic and aggressive, and include other antiandrogen therapies (e.g., androgen receptor–signaling inhibitor) and chemotherapy.

Renal Cell Carcinoma

A. General Characteristics

1. It is twice as common in men as in women.
2. RCC comprises about 85% of primary renal cancers (transitional cell of the renal pelvis is the second most common).
3. Most cases are sporadic; less than 2% occur as part of autosomal dominant von Hippel–Lindau syndrome. The pathogenesis is unknown.
4. Usually discovered when localized to kidney or with regional lymph node spread
5. Areas of metastasis include the lung, liver, brain, and bone. Tumor thrombus can invade the renal vein or inferior vena cava, resulting in hematogenous dissemination.

Quick HIT

Up to 20% to 30% of cases of RCC are discovered incidentally on a CT scan or ultrasound performed for other reasons.

B. Risk Factors

1. Cigarette smoking
2. Analgesics (high use), particular phenacetin-containing medications but acetaminophen, NSAIDs, and aspirin have also been implicated
3. Adult polycystic kidney disease
4. Chronic dialysis (multicystic disease develops)

5. Exposure to heavy metals (mercury, cadmium)
6. Hypertension
7. Obesity

C. Clinical Features

1. Hematuria is the most common symptom (gross or microscopic)—occurs in 70% of the patients.
2. Abdominal or flank pain—occurs in 50% of the patients.
3. Abdominal (flank) mass—occurs in 40% of the patients.
4. Findings seen in many neoplasms: Weight loss, fever, anemia of chronic inflammation.
5. Paraneoplastic syndromes (uncommon)—these tumors can ectopically secrete erythropoietin (causing polycythemia), PTH-like hormone (causing hypercalcemia), renin (causing HTN), cortisol (causing Cushing syndrome), or gonadotropins (causing feminization or masculinization).

Quick HIT

The classic triad of hematuria, flank pain, and abdominal mass occurs in less than 10% of patients with RCC.

D. Diagnosis

1. Abdominal CT (with and without contrast)—optimal test for diagnosis and staging; perform if ultrasound shows a mass or cysts. Cannot distinguish benign and malignant solid masses, both are usually empirically resected.
2. Renal ultrasound—occasionally used for detection of renal mass and to distinguish from cyst.

E. Treatment

1. Partial nephrectomy (open or laparoscopic) can be used for smaller tumors, particularly when bilateral or with associated genetic syndrome, to save renal parenchyma and function.
2. Radical nephrectomy (excision of kidney and adrenal gland, including Gerota fascia with excision of nodal tissue along the renal hilum) when

any invasion into surrounding vasculature or adipose is noted.

3. For advanced disease, debulking surgery and adjuvant chemotherapy is often used.

Quick HIT

Transitional cell carcinoma accounts for 90% of all bladder cancers. Other types are squamous cell (5%) and adenocarcinoma (2%).

Bladder Cancer

A. General Characteristics

1. Bladder carcinoma is the most common type of tumor of the genitourinary tract; 90% of bladder cancers are transitional cell carcinomas. Transitional cell carcinomas can occur anywhere from the kidney to the bladder (e.g., renal pelvis, ureter), but 90% of these carcinomas are in the bladder.
2. The most common route of spread is direct local extension to surrounding tissues (rather than hematologic/lymphatic dissemination).
3. **It is likely to recur after removal.**
4. Risk factors
   a. Cigarette smoking (the major identified risk factor)
   b. Industrial carcinogens (aniline dye, azo dyes)
   c. Long-term treatment with cyclophosphamide (may cause hemorrhagic cystitis and increase the risk of transitional cell carcinoma)

B. Clinical Features

1. Initial presenting sign is **hematuria** in most cases (painless hematuria is the classic presentation). It is more likely to be gross, but can be microscopic as well.
2. Irritable bladder symptoms, such as dysuria, frequency, and/or urgency.
3. Pain or obstructive symptoms may be seen when carcinoma becomes more invasive.

4. Physical examination is usually unremarkable.

C. Diagnosis

1. Urinalysis and urine culture—to detect RBCs and confirm hematuria as red urine may also be due to various foods or medications (e.g., beets, dyes, phenazopyridine, myoglobin, Serratia) and to rule out infection
2. Urine cytology—to detect malignant cells
3. Cystoscopy and biopsy—definitive test which should be performed in all patients >40 years old or with risk factors for bladder cancer
4. Chest radiograph and CT scan—for staging
5. IVP is superior at detecting certain small tumors of ureter or renal pelvis, it can also be used if CT unavailable

A 57-year-old man presents to his physician for his annual examination. He has a history of hypertension, chronic obstructive pulmonary disease (COPD), and benign prostatic hyperplasia (BPH). On examination, there is hyper-resonance to percussion of both lung fields and a diffusely enlarged, nontender prostate on rectal examination. His blood work is unremarkable, but urine studies show 12 RBCs per high-power field. There are no dysmorphic RBCs or RBC casts, and there are no other cells or protein. He denies any fevers, flank or groin pain, episodes of gross hematuria, or dysuria. A repeat urinalysis 1 week later confirms the presence of microscopic hematuria, and his urine culture is negative. He elects to undergo further workup with a CT scan of the abdomen and pelvis with and without contrast, which is unremarkable.

What is the next step in management?

A. Measure PSA
B. Transrectal ultrasound and biopsy of the prostate
C. Intravenous pyelogram
D. Renal biopsy
E. Cystoscopy
F. Reassurance

- **The answer is E: Cystoscopy.** Microscopic hematuria is defined as ≥3 RBCs per high-power field on urine sediment microscopy, and should be confirmed with a repeat study given the high incidence of transient hematuria (which is usually benign but in older patients is still associated with an increased risk of malignancy). **(D)** Glomerulonephritis is a potential cause of hematuria and may lead to a renal biopsy if suspected, but in this case it is unlikely given that there were no dysmorphic RBCs, RBC casts, or other suggestive findings. In the absence of infection or glomerular disease, urine cytology (to screen for infections and neoplasms) and a CT scan (to screen for nephrolithiasis, renal neoplasms, etc.) should be

performed. **(C)** An IV pyelogram may be used to visualize the urinary tract, but a CT scan is a better imaging modality and was already performed in this case. The next step is therefore cystoscopy, which will help to visualize the bladder for cancer. Remember that in microscopic hematuria, in the absence of an identifiable cause (infection or glomerular disease), all patients should receive radiologic imaging of the urinary tract and cystoscopy. **(A, B)** This patient has a history of BPH and consistent findings on examination (diffusely enlarged prostate), making prostate cancer a less likely explanation for this patient's hematuria. PSA screening may be discussed with the patient in the future, but a cystoscopy needs to be performed next. **(F)** In the presence of BPH, new fragile blood vessels form and may rupture causing hematuria; however, more serious causes of hematuria still need to be ruled out.

D. Treatment (depends on the stage of the disease)

1. For surgical candidates, transurethral resection of bladder tumor (TURBT) is used for noninvasive disease, whereas chemotherapy with cystectomy is used for muscle-invasive disease. There is also a role for radiation therapy and systemic chemotherapy for certain patients.

Testicular Cancer

A. General Characteristics

1. Most common in men 20 to 35 years of age, but can occur in men of any age
2. Has a relatively high cure rate compared with other cancers
3. Types
   a. Germ cell tumors (account for 95% of all testicular cancers)—most common in men 20 to 40 years of age; curable in >95% of the cases
      - Seminomas (35%)—most common; slow growth and late invasion; most radiosensitive
      - Nonseminomatous (65%)—usually contain cells from at least two of the following four types (mixed cell type): embryonal carcinoma (high malignant potential, hemorrhage and necrosis are

common; metastases to the abdominal lymphatics and the lungs may occur as an early event); choriocarcinoma (most aggressive type; rare; metastases usually occur by time of diagnosis); teratoma (rarely metastasize); yolk sac carcinoma (rare in men, usually occurs in young boys)

b. Nongerm cell tumors (account for 5% of all testicular cancers)—are usually benign.
   - Leydig cell tumors are hormonally active—most are benign and are treated with surgery. Prognosis is poor if metastasis occurs. They may secrete a variety of steroid hormones, including estrogen and androgens, and are associated with precocious puberty in children and gynecomastia in adults
   - Sertoli cell tumors are usually benign

Quick HIT

In a patient with a scrotal mass, perform a careful physical examination to determine its site of origin because testicular cancers are almost always malignant, whereas extratesticular tumors within the scrotum are almost always benign.

B. Risk Factors

1. Cryptorchidism—surgical correction reduces but does not eliminate risk
2. Klinefelter syndrome

C. Clinical Features

1. Painless mass/lump/firmness of the testicle—because of lack of pain, may go unnoticed by the patient until advanced.
2. While pain is rare, a “dull ache” in the pelvis is often described.
3. Gynecomastia may be present because some of the nonseminomatous germ cell tumors produce gonadotropins.

D. Diagnosis

1. Physical examination (testicular mass)
2. Testicular ultrasound—initial test for localizing the tumor

3. Tumor markers—helpful in diagnosis, staging, and monitoring response to therapy
   a. β-hCG
      - Always elevated in choriocarcinoma
      - May be elevated in other types of nonseminomatous germ cell tumors as well
   b. AFP
      - Increased in embryonal tumors (in 80% of the cases)
      - Choriocarcinoma and seminoma never have an elevated AFP
4. CT scan and chest radiograph for staging
5. Biopsy is NOT performed due to concern for seeding/metastasizing the tumor

> **Quick HIT**
>
> **Differential Diagnosis of Testicular Cancer**
>
> - Varicocele—dilated, tortuous veins in testicle
> - Testicular torsion
> - Spermatocele (testicular cyst)
> - Hydrocele (fluid in testicle)
> - Epididymitis
> - Lymphoma

E. Treatment

1. If testicular cancer is suspected based on physical examination or ultrasound, the testicle should be removed surgically (to confirm diagnosis). An inguinal approach is used because a scrotal incision may lead to tumor seeding of the scrotum.
2. After orchiectomy, perform a CT scan of the chest, abdomen, and pelvis for staging.
3. Perform β-hCG and AFP measurement after orchiectomy for comparison with the preoperative values.
4. Further treatment depends on the histology of the tumor.
   a. Seminoma—inguinal orchiectomy and radiation (very radiosensitive).

b. Nonseminomatous disease—orchiectomy and retroperitoneal lymph node dissection with or without chemotherapy.

Quick HIT

A young man with a firm, painless testicular mass should be presumed to have testicular cancer until proven otherwise.

Penile Cancer

- The peak incidence of this tumor is in men in their seventh decade.
- Circumcision may have a protective effect because penile cancer is very rare in those who have been circumcised.
- It is associated with herpes simplex virus and HPV 18 infection.
- It presents as an exophytic mass on the penis.
- Treatment of the primary disease is local excision.

Quick HIT

Do not confuse testicular cancer with testicular torsion or epididymitis.

Miscellaneous Conditions

Testicular Torsion

- Twisting of the spermatic cord leading to arterial occlusion and venous outflow obstruction; ischemia can lead to testicular infarction.
- Usually seen in adolescents following trauma or physical activity.
- Acute severe testicular pain, swollen and tender scrotum, and an elevated testicle (as twisting occurs, the testicle moves to a higher position in scrotum, the “bell clapper deformity”). Absence of cremasteric reflex is also seen.
- **Testicular ultrasound with Doppler** should be performed immediately, torsion is suggested by the absence of normal arterial pulsations.

- **This is a surgical emergency:** immediate surgical detorsion and orchiopexy to the scrotum (perform bilaterally to prevent torsion in the contralateral testicle). **If surgery is delayed beyond 6 hours, infarction may occur, and the testicle may not be salvageable.**
- Orchiectomy if a nonviable testicle is found.

Quick HIT

Epididymitis may be difficult to differentiate from testicular torsion.

Epididymitis

- Infection of the epididymis. The common offending organism in children and elderly patients is *Escherichia coli*; in young men, sexually transmitted diseases are more common (gonorrhea, *Chlamydia*).
- A swollen, tender testicle; dysuria; fever/chills; scrotal pain; and a scrotal mass. Intact cremasteric reflex.
- Rule out testicular torsion with ultrasound, and administer antibiotics.

Fluids, Electrolytes, and Acid–Base Disorders 8

Mark D. Duncan

Volume Disorders

Approach to Volume Disorders

A. Normal Body Fluid Compartments

1. Men: total-body water (TBW) = 60% of body weight (Figure 8-1)
2. Women: TBW = 50% of body weight
3. Percentage of TBW decreases with age and increasing obesity (TBW decreases because fat contains very little water)
4. Distribution of water
   a. Intracellular fluid (ICF) is two-thirds of TBW (or 40% of body weight)—the largest proportion of TBW is in skeletal muscle mass
   b. Extracellular fluid (ECF) is one-third of TBW (or 20% of body weight)
      - Plasma is one-third of ECF, one-twelfth of TBW, and 5% of body weight
      - Interstitial fluid is two-thirds of ECF, one-fourth of TBW, and 15% of body weight

Quick HIT

For body fluid compartments, remember the 60-40-20 rule.
- TBW is 60% of body weight (50% for women).
- ICF is 40% of body weight.
- ECF is 20% of body weight (interstitial fluid 15% and plasma 5%).

5. Water exchange
   a. Normal intake: Average 1,500 mL in fluids taken PO per day; 500 mL in solids or product of oxidation
   b. Normal output
      - From 800 to 1,500 mL in urine per day is the normal range. Minimum urine output to excrete products of catabolism is about 500 to 600 mL/day, assuming normal renal concentrating ability
      - Output of 250 mL/day occurs in stool
      - From 600 to 900 mL/day in insensible losses occurs. This is highly variable but increases with fever, sweating, hyperventilation, and tracheostomies (unhumidified air)—see below
   c. Remember the Starling equation and forces: fluid shift depends on hydrostatic and oncotic pressures
   d. As osmolality of fluids (ECF or ICF) changes (e.g., hyponatremia, hyperglycemia), water will shift freely through the permeable cell membranes to maintain isotonicity, which will lead to a change in the distribution of TBW

Quick HIT

The differential for oliguria is the same as AKI:
- Prerenal causes (poor blood flow to kidney, such as hypovolemia, heart disease, liver disease, etc.)
- Intrinsic renal problem (glomerular, tubular, interstitial, or vascular)
- Postrenal obstruction (place a Foley catheter)

B. Assessing Volume Status

1. There is a lot of variability in certain physical examination maneuvers and diagnostic studies used to help determine volume status. None of these replace a good history and clinical judgment.
2. Tracking input and output is not an exact science either because there is no accurate way of calculating insensible losses. Monitoring urine output is very important in the assessment of volume status: **Normal urine output in infants is more than 1.0 mL/kg/hr, while normal urine output for an adult is generally regarded as 0.5 to 1.0 mL/kg/hr.** As long as the kidneys are functioning properly and in the absence of obstruction, low urine output reflects an appropriate

response to low renal blood flow, either from volume depletion or low effective circulative volume (as in CHF, cirrhosis).

3. Daily weights may give a more accurate assessment of volume trends.

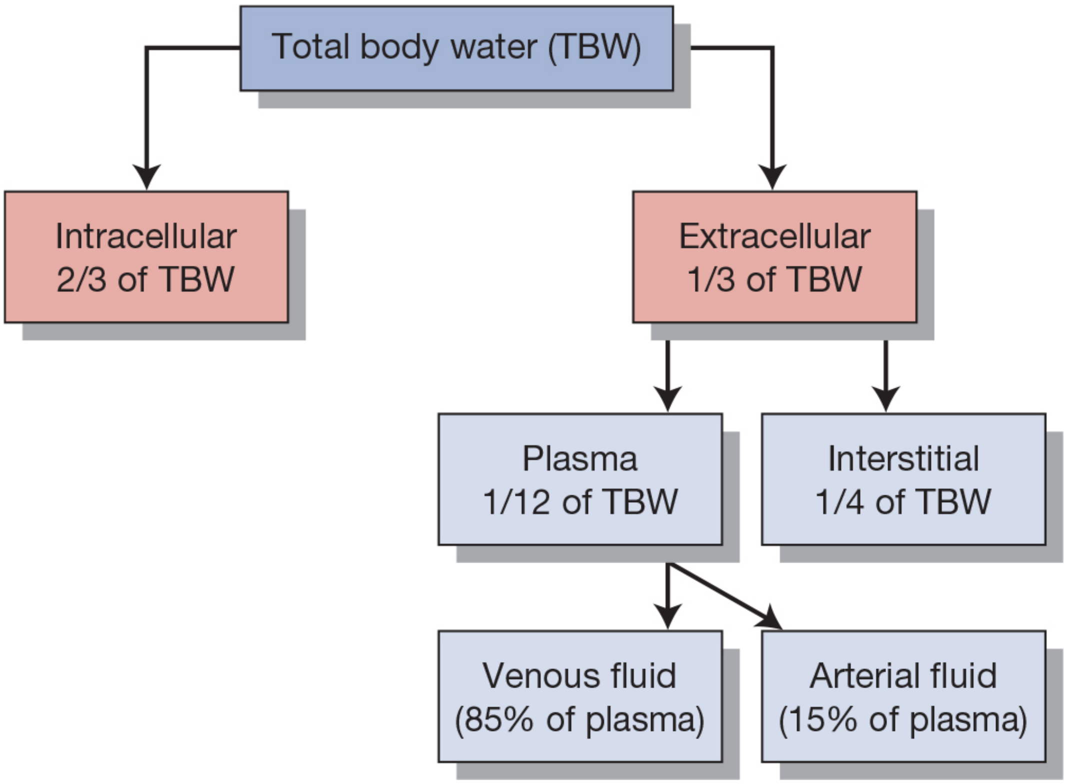


FIGURE 8-1 **Body fluid compartments.**

C. Fluid Replacement Therapy

1. Crystalloid solutions (e.g., normal saline [NS], lactated Ringer's (LR), Plasma-Lyte),
   a. Uses: most common resuscitative fluid used to increase intravascular volume
   b. Choosing the type of crystalloid solution:
      - There are some data suggesting a modest benefit of buffered crystalloid solutions (LR) over NS, especially in regard to renal injury. However, other trials have not consistently shown this same benefit.
      - NS in large volumes may create a hyperchloremic, nonanion gap metabolic acidosis and AKI.

- Ultimately, the choice of fluid is likely less important than the amount.

Quick HIT

If a patient is receiving hypotonic solutions (1/2 NS, 1/4 NS), water is initially transferred from the ECF to intracellular space to equilibrate osmotic pressures in both compartments.

2. Dextrose-containing fluids
   a. Used in patients with hypoglycemia or prolonged NPO states, though should not be used in patients with uncontrolled diabetes.
   b. D51/2 NS is often used as a maintenance IV fluid, though may contribute to iatrogenic hyponatremia.
   c. D5W can safely provide free water to patients, and is commonly used for the treatment of hypernatremia or in patients with hyponatremia that are correcting their serum sodium too quickly.
3. Colloid solutions (e.g., albumin)
   a. The use of colloid solutions, as opposed to crystalloids, in the setting of acute resuscitation has been controversial. While they do, in theory, provide intravascular oncotic pressure which saline solutions do not, they have not shown clear benefit in large trials, are expensive, and may cause harm in critically ill and TBI patients due to shift of albumin into the interstitial space. They are not used in volume resuscitation in all patients, but have a role in certain situations (e.g., cirrhotic patients with SBP or after large-volume paracentesis).
   b. Blood products
   c. Massive transfusion protocols are used in cases of hemorrhagic shock. Other IV fluids alone should not be used instead of blood products.

Hypovolemia

A. Causes

1. Inadequate intake

2. Trauma, open wounds, sequestration of fluid into soft tissue injuries
3. GI losses due to vomiting, nasogastric suction, diarrhea, fistula drainage, etc.
4. Polyuria—for example, diabetic ketoacidosis (DKA)
5. Third-spacing due to ascites, effusions, bowel obstruction, crush injuries, burns
6. Sepsis, intra-abdominal and retroperitoneal inflammatory processes
7. Insensible losses—losses through the skin (75%) and the respiratory tract (25%)

B. Clinical Features

1. CNS findings: mental status changes, sleepiness, apathy, coma
2. Cardiovascular findings (due to decrease in plasma volume): orthostatic hypotension, tachycardia, decreased pulse pressure, decreased central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP), can also be thought of in terms of the Classes of Hypovolemic Shock:
   a. Class I (<750 mL estimated blood loss [EBL]): Vital signs normal, minimal symptoms
   b. Class II (750 to 1,500 mL EBL): Tachycardia and tachypnea, normal BP, decreased urine output
   c. Class III (1,500 to 2,000 mL EBL): Above symptoms and hypotension at rest, very decreased urine output (<20 cc/hr)
   d. Class IV (>2,000 mL EBL): Above symptoms and little to no urine output
   e. Note that the initial signs of hypovolemia/hemorrhage may be subtle including tachycardia with a normal BP, once BP falls usually at least 30% blood volume has been lost
3. Skin: poor skin turgor, hypothermia, cool and pale extremities (due to vasoconstriction), dry tongue and axilla
4. Ileus, weakness
5. Decreased urine output, either compensatory to conserve fluid or as a manifestation of acute renal failure due to prerenal azotemia (fractional excretion of sodium <1% and/or BUN/creatinine >20)
6. Remember that once these symptoms of end-organ damage are present, patient has entered shock and typically has lost 20% to 30% of their total blood volume

C. Diagnosis

1. Monitor urine output and daily weights. If the patient is critically ill and has cardiac or renal dysfunction, consider placing a Swan–Ganz catheter (to measure CVP and PCWP).
2. Elevated serum sodium, low urine sodium, and a BUN/Cr ratio of >20:1 suggest hypoperfusion to the kidneys, which usually (not always) represents hypovolemia.
3. Hematocrit: 3% increase for each liter of deficit, unless otherwise lowered due to hemorrhage. However note that hematocrit may be **normal** in acute blood loss as fluid has not yet had time to transition from interstitial space back to vasculature.
4. The concentration of formed elements in the blood (RBCs, WBCs, platelets, plasma proteins) increases with an ECF deficit and decreases with an ECF excess.

D. Treatment

1. Correct volume deficit.
   a. Use bolus to achieve euvolemia. Begin with isotonic solution (lactated Ringer's or NS).
   b. Targeting euvolemia via frequent monitoring of HR, BP, urine output, and weight is essential.
   c. **Maintain urine output at 0.5 to 1 mL/kg/hr.**
   d. Blood loss—replace blood loss with crystalloid at a 3:1 ratio. As stated above, initial hematocrit may not reflect actual quantity of blood lost. Therefore, in the acute trauma setting, replace the EBL.
2. Maintenance fluid.
   a. D51/2 NS solution with 20 mEq KCl/L is a common adult maintenance fluid, though should be monitored for iatrogenic hyponatremia.
   b. There are two methods of calculating the amount of maintenance fluid (see Clinical Pearl 8-1).

Quick HIT

Do **not** combine bolus fluids with dextrose (which can lead to hyperglycemia) or potassium (which can lead to hyperkalemia).

Quick HIT

Most cases of edema result from renal sodium retention.

Hypervolemia

A. Causes

1. Iatrogenic (parenteral overhydration)
2. Fluid-retaining states: CHF, nephrotic syndrome, cirrhosis, ESRD

CLINICAL PEARL 8-1

Calculation of Maintenance Fluids

- 100/50/20 rule:
  - 100 mL/kg for first 10 kg, 50 mL/kg for next 10 kg, 20 mL/kg for every 1 kg over 20
  - Divide total by 24 for hourly rate
  - For example, for a 70-kg man: 100 × 10 = 1,000; 50 × 10 = 500, 20 × 50 kg = 1,000. Total = 2,500. Divide by 24 hours: **104 mL/hr**
- 4/2/1 rule:
  - 4 mL/kg for first 10 kg, 2 mL/kg for next 10 kg, 1 mL/kg for every 1 kg over 20
  - For example, for a 70-kg man: 4 × 10 = 40; 2 × 10 = 20; 1 × 50 = 50. Total = **110 mL/hr**

B. Clinical Features

1. Weight gain
2. Vital signs in some cases may show hypotension and hemodynamic instability (as in decompensated heart failure) or tachypnea and hypoxia if pulmonary edema is present.
3. Physical examination signs of fluid overload:
   a. Peripheral (usually pitting) edema (pedal or sacral)
   b. Ascites: flank bulging and dullness (most sensitive), fluid wave (most specific), and shifting dullness
   c. Pulmonary edema: manifesting as rales or dullness at the lung bases

d. Jugular venous distention: may be difficult to evaluate in obese patients or if TR is present
4. Labs may show low hematocrit and albumin concentration, hyponatremia
5. Elevated CVP and PCWP on Swan–Ganz Catheter

Quick HIT

Signs of Volume Overload

- Elevated jugular venous pressure
- Pulmonary rales—due to pulmonary edema
- Peripheral edema

C. Treatment

1. Fluid restriction
2. Judicious use of diuretics
3. Monitor urine output and daily weights, and consider Swan–Ganz catheter placement depending on the patient's condition.
4. If patient is hemodynamically unstable and initial attempts are unsuccessful, urgent dialysis may rarely be indicated (recall volume overload is one of the AEIOU indications, see Chapter 7).

Sodium

Overview of Sodium Homeostasis

A. Salt and Water Regulation

1. Na^+ regulation is intimately associated with water homeostasis, yet it is regulated by independent mechanisms.
2. Changes in Na^+ **concentration** are a reflection of water homeostasis, whereas changes in Na^+ **content** (and subsequently, fluid volume) are a reflection of Na^+ homeostasis.

3. Disturbance of Na^+ balance may lead to hypovolemia or hypervolemia, and disturbance of water balance may lead to hyponatremia or hypernatremia.

B. Sodium Homeostasis

1. Sodium is actively pumped out of cells and is therefore restricted to the extracellular space. It is the main osmotically active cation of the ECF.
2. An increase in sodium intake results in an increase in ECF volume, which results in an increase in GFR and sodium excretion. This occurs partially through release of ANP and BNP by the heart and decrease of renal renin release, which together promote natriuresis and inhibit norepinephrine, epinephrine, aldosterone, and ADH release.
3. A decline in the extracellular circulating volume results in a decreased GFR and a reduction in sodium excretion. This is a response to the sympathetic nervous system increasing cardiac output as well as a decrease in renal perfusion pressure resulting in activation of the renin–angiotensin–aldosterone system. Aldosterone increases sodium reabsorption and potassium secretion from the late distal tubules.
4. Diuretics inhibit Na^+ reabsorption through various mechanisms in the renal tubular system. Furosemide and other loop diuretics inhibit the Na^+–K^+–Cl^- transporter in the thick ascending limb of the loop of Henle, whereas thiazide diuretics inhibit the Na^+–Cl^- cotransporter at the early distal tubule. However, the majority of Na^+ reabsorption occurs in the proximal tubule.

C. Water Homeostasis

1. Osmoreceptors in the hypothalamus are stimulated by plasma hypertonicity (usually >295 mOsm/kg); activation of these stimulators produces thirst.
2. Hypertonic plasma also stimulates the secretion of antidiuretic hormone (ADH) from the posterior pituitary gland. When ADH binds to V_2 receptors in the renal collecting ducts, water channels are synthesized and more water is reabsorbed.
3. ADH is suppressed as plasma tonicity decreases.
4. Ultimately, the amount of water intake and output (including renal, GI, and insensible losses from the skin and the respiratory tract) must be

equivalent over time to preserve a steady state.
5. When a steady state is not achieved, hyponatremia or hypernatremia usually occurs.

Quick HIT

- Aldosterone increases sodium reabsorption, water then follows.
- ADH increases water reabsorption alone.

Hyponatremia

A. General Characteristics

1. This refers to too much water in relation to sodium in the serum.
2. It is typically defined as a plasma Na^+ concentration <135 mEq/L.
3. Symptoms usually begin when the Na^+ level falls to <120 mEq/L. An important exception is increased intracranial pressure (ICP) (e.g., after head injury). As ECF osmolality decreases, water shifts into brain cells, further increasing ICP. (Therefore, it is critical to keep serum sodium normal or slightly high in such patients.)

Quick HIT

- Hyponatremia and hypernatremia are caused by too much or too little **water**.
- Hypovolemia and hypervolemia are caused by too little or too much **sodium**.

B. Causes and Classification (based on serum osmolality)

1. **Hypotonic hyponatremia**—"true hyponatremia"—serum osmolality <280 mOsm/kg (can be measured or calculated using sodium, BUN, and glucose)
   a. Hypovolemic
      - Low urine sodium (<10 mEq/L)—implies increased sodium retention by the kidneys to compensate for **extrarenal losses** (e.g.,

diarrhea, vomiting, nasogastric suction, diaphoresis, third-spacing, burns, pancreatitis) **of sodium-containing fluid.**
- High urine sodium (>20 mEq/L)—renal salt loss is likely due to tubular dysfunction—for example, diuretic excess, decreased aldosterone (i.e., RTA type IV, causes include ACE inhibitors and ARBs), ATN.

b. Euvolemic—no evidence of ECF expansion or contraction on clinical grounds
- SIADH: Causes are numerous and include CNS pathologies, malignancy (most commonly small cell lung cancer), surgery (postoperative hyponatremia), drugs (e.g., SSRIs, oxytocin, carbamazepine, haloperidol, cyclophosphamide, certain antineoplastic agents), infections (HIV, pulmonary infections), and more
- Hypothyroidism: mechanism not fully understood
- Adrenal insufficiency: cause is multifactorial
- Psychogenic polydipsia (urine osmolality <100)
- Administration/intake of a relative excess of free water—if a patient is given D5W (or other hypotonic solution) to replace fluids, or if water alone is consumed after intensive exertion (with profuse sweating)
- Low dietary solute intake: kidneys excrete free water by diluting urine, however all urine must contain some solute; therefore individuals with poor diets (beer drinkers, elderly persons with “tea and toast” diet) with a relative deficiency of these solutes will be limited in daily free water excretion. This will also have a low urine osmolality <100

c. Hypervolemic (low urine sodium)—This is due to water-retaining states. The relative excess of water in relation to sodium results in hyponatremia.
- CHF
- Nephrotic syndrome (renal failure)
- Liver disease

Quick HIT

Excessive water intake alone rarely leads to hyponatremia because the kidneys have a great capacity to excrete water.

2. Isotonic hyponatremia (pseudohyponatremia)
   a. An increase in plasma solids (e.g., proteins or lipids) artificially lowers the plasma sodium concentration measurement via **laboratory artifact**, but the **amount** of sodium in plasma is normal (hence, **pseudo**hyponatremia).
   b. This can be caused by any condition that leads to elevated protein or lipid levels.
3. Hypertonic hyponatremia
   a. Caused by the presence of osmotic substances that cause an **osmotic shift of water out of cells.** These substances cannot cross the cell membrane and therefore create osmotic gradients
   b. These substances include:
      - Glucose—**Hyperglycemia** increases osmotic pressure, and water shifts from cells into ECF leading to a dilutional hyponatremia. For every 100 mg/dL increase in blood glucose level above normal, the serum sodium level decreases about 3 mEq/L. Note that the actual sodium content in the ECF is unchanged.
      - Mannitol, sorbitol, glycerol, maltose
      - Radiocontrast agents

Quick HIT

As opposed to acute water intoxication, when hyponatremia develops gradually (over a few days), the clinical features do not appear until a relatively lower sodium level is reached.

C. Clinical Features

1. **Neurologic symptoms predominate**—caused by "water intoxication"—osmotic water shifts, which leads to increased ICF volume, specifically brain cell swelling or cerebral edema
   a. Headache, delirium, irritability

b. Muscle twitching, weakness
c. Hyperactive deep tendon reflexes

2. Increased ICP, seizures, coma
3. GI—nausea, vomiting, ileus, watery diarrhea
4. Cardiovascular—hypertension due to increased ICP
5. Increased salivation and lacrimation
6. Oliguria progressing to anuria—**may not be reversible if therapy is delayed and acute renal failure develops**

D. Diagnosis

1. Plasma osmolality—low in a patient with true hyponatremia (Figure 8-2)
2. Urine osmolality
   a. Low if the kidneys are responding appropriately by diluting the urine—for example, primary polydipsia
   b. Elevated if there are increased levels of ADH—for example, SIADH, CHF, and hypothyroidism
3. Urine sodium concentration
   a. Urine Na^+ should be low in the setting of hyponatremia
   b. Urine Na^+ concentration >40 mmol/L is consistent with SIADH, salt-wasting nephropathy or hypoaldosteronism. Diuretics may produce this as well
   c. Urine Na^+ concentration <20 mmol/L is consistent with hypovolemia

A 59-year-old woman presents with fatigue and weakness and is found to have a serum sodium of 126 mEq/L. Her medical history includes GERD and anxiety, and her medications include aspirin, pantoprazole, and sertraline. Her examination is unremarkable. Her urine studies reveal a urine sodium of 74 mEq/L and a urine osmolality of 420 mOsm/kg.

Which of the following is the most likely diagnosis?

A. Psychogenic polydipsia
B. Heart failure
C. SIADH
D. Hypovolemia
E. Adrenal insufficiency

- **The answer is C: SIADH.** The patient presents with moderate hyponatremia, and her urine osmolality is >100 which essentially rules out **(A)** psychogenic polydipsia as well as low solute intake (tea and toast or beer potomania). Her urine sodium is >40, and in the absence of diuretic use this is not suggestive of diagnoses of (**D**) hypovolemia or (**B**) heart failure, which would have a low urine sodium <20. Thus, these findings are suggestive of SIADH, which may be caused by her SSRI sertraline. (**E**) Adrenal insufficiency is another cause of euvolemic hyponatremia, but there is nothing to suggest this diagnosis in the vignette.

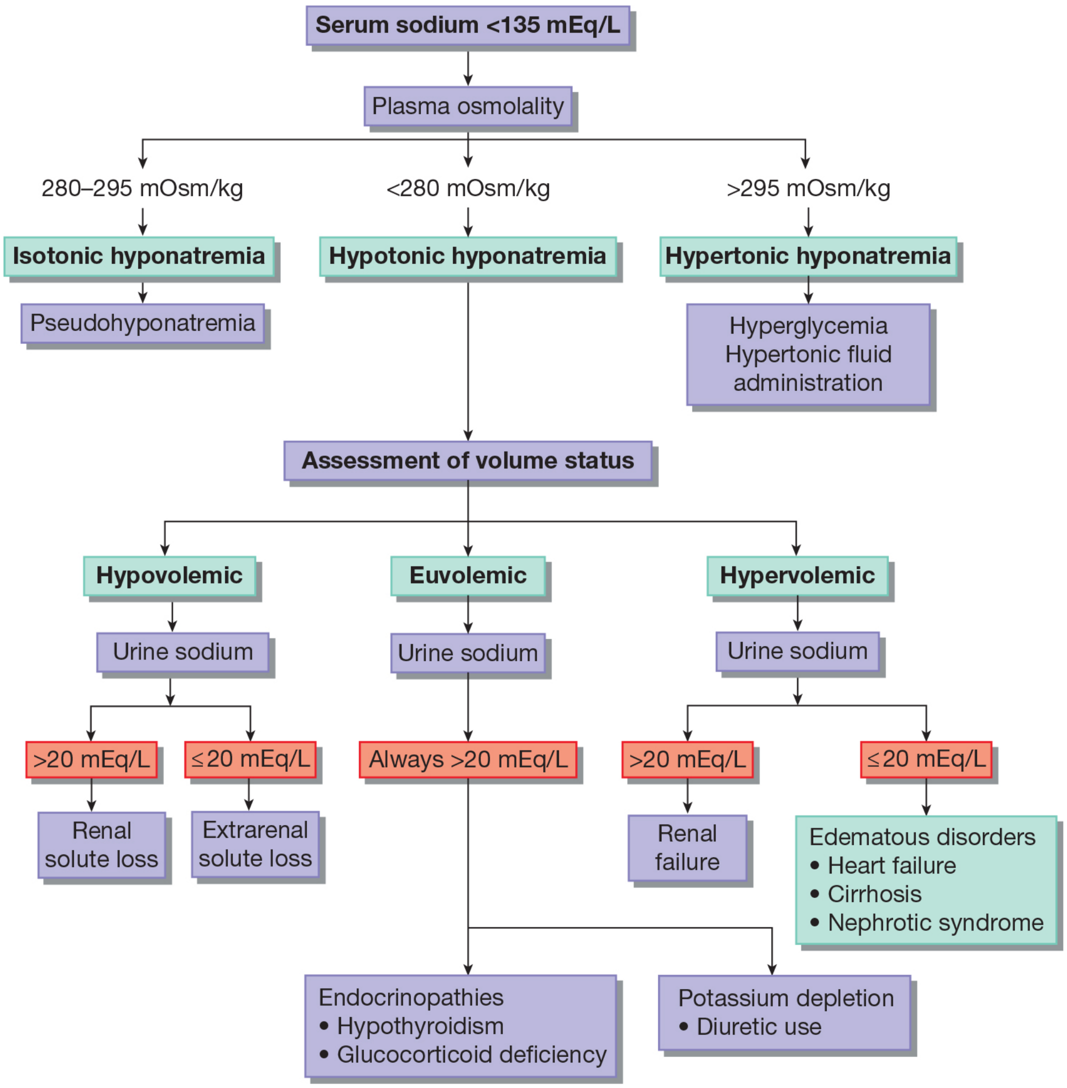


FIGURE 8-2 **Evaluation of hyponatremia.**

Quick HIT

Most cases of hypernatremia are due to the following types of free water loss:

- Nonrenal loss: insensible loss, GI tract (diarrhea)
- Renal loss: osmotic diuresis, diabetes insipidus

E. Treatment

1. Isotonic and hypertonic hyponatremias—diagnose and treat the underlying disorder
2. Hypotonic hyponatremia

a. Depends on the underlying condition, which should always be addressed, as well as severity (mild Na 130–134, moderate 120–129, and severe <120) and the chronicity (acute hyponatremia can be corrected more quickly)
b. The majority of patients should have free water restriction
c. Volume status will determine diuresis versus giving IVF
d. Severe (Na^+ <120 mmol/L) or if symptomatic—give hypertonic saline to increase serum sodium by 1 to 2 mEq/L/hr until symptoms improve
   - Hypertonic saline rapidly increases the tonicity of ECF.
   - Do not increase sodium more than 8 mmol/L during the first 24 hours. An overly rapid increase in serum sodium concentration may produce **central pontine demyelination**
   - Rate of correction: Maximum 8 mEq/L in 24 hours to prevent overcorrection and osmotic demyelination syndrome, however in symptomatic patients aim for correcting 4 to 6 mEq/L in first 6 hours. Make sure to check sodium levels frequently

Hypernatremia

A. General Characteristics

1. Defined as a plasma Na^+ concentration >145 mmol/L
2. Refers to excess sodium in relation to water; can result from water loss or, rarely, sodium infusion

Quick HIT

Excessively rapid correction of hypernatremia can lead to **cerebral edema** as water shifts into brain cells. Therefore, the rate of correction should not exceed 12 mEq/L/day (should be <8 mEq/L in the first 24 hours).

3. Assess ECF volume clinically, as follows (Figure 8-3):
   a. Hypovolemic hypernatremia (sodium stores are depleted, but relatively more water has been lost)
      - Renal loss—from diuretics, **osmotic diuresis** (most commonly due to glycosuria in diabetics), renal failure

- Extrarenal loss—from **diarrhea,** diaphoresis, respiratory losses

b. Isovolemic hypernatremia (sodium stores normal, water lost)

- **Diabetes insipidus: central (usually due to CNS pathologies) or peripheral (causes include lithium toxicity, hypercalcemia, hypokalemia, renal disease, drugs)**
- Insensible respiratory (tachypnea)

c. Hypervolemic hypernatremia (sodium excess)—occurs infrequently

- Iatrogenic—most common cause of hypervolemic hypernatremia (e.g., large amounts of parenteral $NaHCO_3$, TPN)
- Exogenous glucocorticoids
- Cushing syndrome
- Saltwater drowning
- Primary hyperaldosteronism

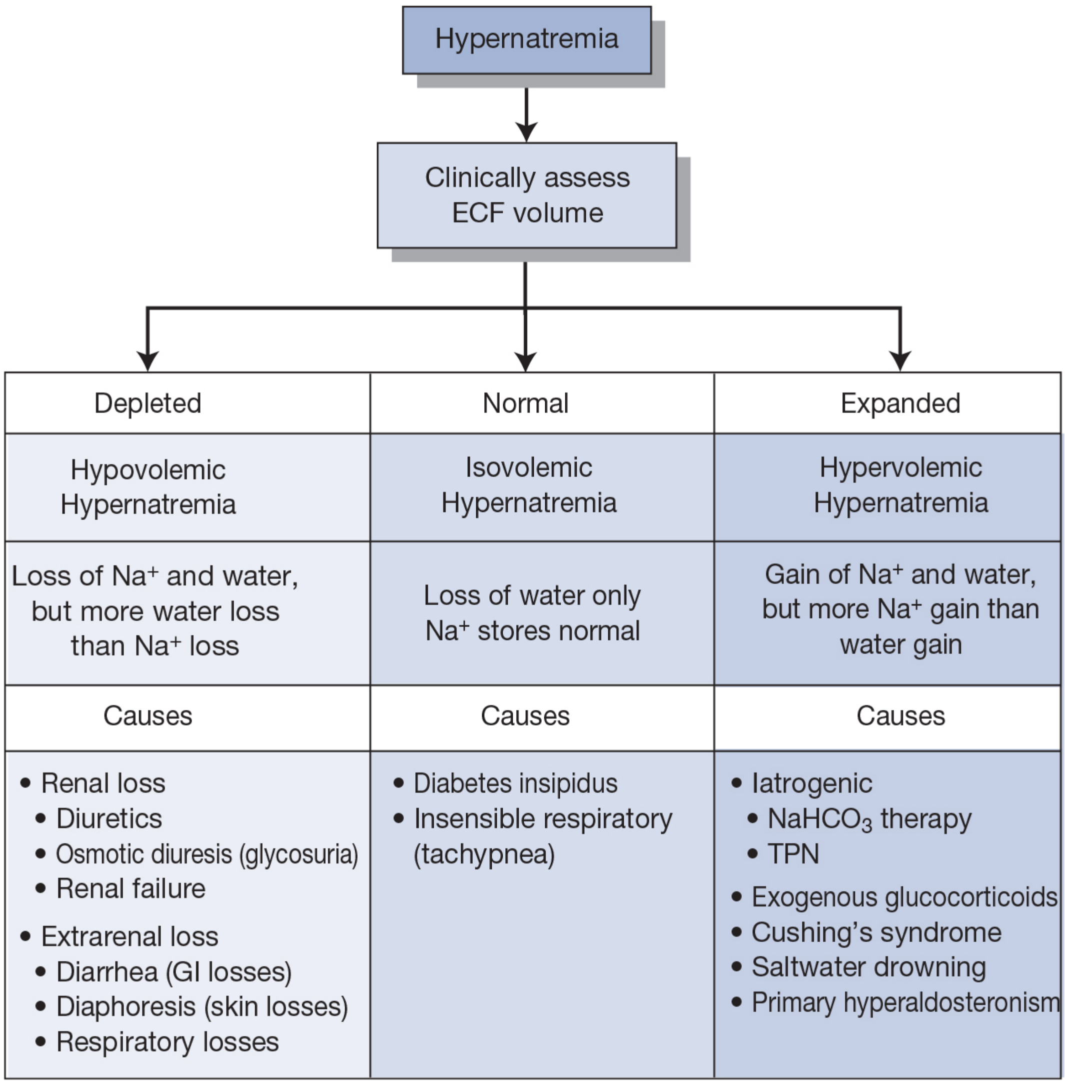


FIGURE 8-3 **Evaluation of hypernatremia.**
(Adapted with permission from Glassock RJ, Massry SG. *Massry and Glassock's Textbook of Nephrology*. 4th ed. Lippincott Williams & Wilkins; 2000.)

Quick HIT

Clinical features of hypernatremia are secondary to osmotic effects on the brain (water shifts out of brain cells, leaving them dehydrated). Symptoms are more prominent and severe when sodium levels increase rapidly.

B. Clinical Features

1. Neurologic symptoms predominate

a. Altered mental status, restlessness, weakness, focal neurologic deficits
b. Can lead to confusion, seizures, coma
2. Tissues and mucous membranes are dry; salivation decreases

C. Diagnosis

1. Urine volume should be low if the kidneys are responding appropriately.
2. Urine osmolality should be >800 mOsm/kg.
3. Desmopressin should be given to differentiate nephrogenic from central diabetes insipidus if diabetes insipidus is suspected (see Chapter 4).

D. Treatment

1. Hypovolemic hypernatremia—Give isotonic NaCl to achieve euvolemia and restore hemodynamics initially. Correction of hypernatremia can wait until the patient is hemodynamically stable, then replace the free water deficit (see Clinical Pearl 8-1).
2. Isovolemic hypernatremia—Patients with diabetes insipidus require vasopressin (nephrogenic DI, unless hereditary, is rarely complete), low sodium diet, and thiazide diuretics. Prescribe oral fluids, or if the patient cannot drink, give D5W.
3. Hypervolemic hypernatremia—Give diuretics (such as furosemide, to correct volume status) and D5W (to achieve normal sodium concentration) to remove excess sodium. Dialyze patients with renal failure.

Quick HIT

Calculating free water deficit
Water deficit = TBW (1 − actual Na^+ ÷ desired Na^+)

Calcium

Calcium Metabolism

A. Normal Serum Calcium

The normal serum calcium (Ca^{2+}) range is 8.5 to 10.5 mg/dL. Calcium balance is regulated by hormonal control, but the levels are also affected by albumin and pH.

1. Albumin
   a. Calcium in plasma exists in two forms:
      - Protein-bound form: most calcium ions are bound to albumin, so the total calcium concentration fluctuates with the protein (albumin) concentration.
      - Free ionized form: **physiologically active** fraction; under tight hormonal control (PTH), **independent of albumin levels.**

   b. In hypoalbuminemia, the total calcium is low, but ionized calcium is normal, and can be estimated by the following formula: total calcium —(serum albumin × 0.8).
2. Changes in pH alter the ratio of calcium binding. An increase in pH increases the binding of calcium to albumin. Therefore, in alkalemic states (especially acute respiratory alkalosis), total calcium is normal, but ionized calcium is low and the patient frequently manifests the signs and symptoms of hypocalcemia.

B. Hormonal Control

1. PTH—↑ plasma Ca^{2+} and ↓ plasma PO_4^{3-} by acting on:
   a. Bone: ↑ bone resorption
   b. Kidney: ↑ Ca^{2+} reabsorption, ↓ PO_4^{3-} reabsorption
   c. Gut: activation of vitamin D
2. Calcitonin—↓ plasma Ca^{2+} and ↓ plasma PO_4^{3-} by acting on:
   a. Bone: ↓ bone resorption
   b. Kidney: ↓ Ca^{2+} reabsorption, ↑ PO_4^{3-} reabsorption
   c. Gut: ↓ postprandial Ca^{2+} absorption

3. Vitamin D—↑ plasma Ca^{2+} and ↑ plasma PO_4^{3-} by acting on:
   a. Bone: ↑ bone resorption
   b. Kidney: ↑ Ca^{2+} reabsorption, ↑ PO_4^{3-} reabsorption
   c. Gut: ↑ Ca^{2+} absorption, ↑ PO_4^{3-} reabsorption

Quick HIT

Maintenance of calcium balance is a function of PTH, calcitonin, and vitamin D, and their target organs bone, kidney, and gut.

Hypocalcemia

A. Causes

1. Hypoparathyroidism (most common cause)—usually due to surgery on the thyroid gland (with damage to nearby parathyroids)
2. Renal insufficiency—mainly due to decreased production of 1,25-dihydroxy vitamin D.
3. Vitamin D deficiency
4. Hyperphosphatemia—PO_4^{3-} precipitates with Ca^{2+} resulting in calcium phosphate deposition
5. Hypomagnesemia—results in decreased PTH secretion. Malabsorption—for example, short bowel syndrome, leading to low vitamin D or magnesium
6. Pseudohypoparathyroidism—autosomal recessive disease causing congenital end-organ resistance to PTH (so PTH levels are actually high); also characterized by mental retardation and short metacarpal bones
7. Hypoalbuminemia—clinically irrelevant as ionized (metabolically active) component is normal
8. Alkalemia—as above, increase in pH causes increased calcium binding, serum levels will be normal but clinically important as ionized fraction is low
9. Acute pancreatitis—deposition of calcium deposits lowers serum Ca^{2+} levels
10. Blood transfusion (with citrated blood)—calcium binds to citrate

11. Osteoblastic metastases
12. DiGeorge syndrome—caused by a deletion on chromosome 22. Absence of thymic shadow on chest x-ray

> ***Quick* HIT**
>
> Ionized calcium may be low with normal serum calcium levels in acute alkalotic states.

B. Clinical Features

1. Asymptomatic
2. Rickets and osteomalacia
3. Increased neuromuscular irritability
   a. Numbness/tingling—circumoral in fingers, in toes
   b. Tetany
      - Hyperactive deep tendon reflexes
      - *Chvostek sign*—tapping a facial nerve leads to a contraction (twitching) of facial muscles
      - *Trousseau sign*—inflate BP cuff to a pressure higher than the patient's systolic BP for 3 minutes (occludes blood flow in forearm). This elicits carpal spasms.

   c. Seizures
4. Basal ganglia calcifications
5. Cardiac manifestations
   a. Arrhythmias
   b. Prolonged QT interval on ECG—hypocalcemia should always be in the differential diagnosis for a prolonged QT interval

> ***Quick* HIT**
>
> Hospitalized patients frequently have low serum albumin concentrations. Therefore, if you see a low calcium level, look at the albumin level (it is usually low as well). A low serum **ionized calcium** level is much less common.

A 21-year-old college student presents to the emergency department with severe epigastric abdominal pain that radiates to her back. She is nauseous but has not vomited, and denies any diarrhea. She is admitted and her laboratory values show an elevated serum amylase and lipase.

Which of the following electrolyte abnormalities is associated with this disease?

A. Hypernatremia
B. Hyponatremia
C. Hyperkalemia
D. Hypokalemia
E. Hypercalcemia
F. Hypocalcemia
G. Hypermagnesemia
H. Hypomagnesemia

- **The answer is F: Hypocalcemia.** This patient likely has acute pancreatitis from alcohol. Acute pancreatitis can cause hypocalcemia due to extravascular binding of calcium to free fatty acids, which surround the pancreas as a result of pancreatic autodigestion by lipase. The other electrolyte abnormalities are not as strongly associated with acute pancreatitis as hypocalcemia. The total calcium level represents both the ionized form (the physiologically active form) as well as the 45% that is bound to serum proteins (primarily albumin). Therefore, patients with low albumin will have a low total calcium but a normal ionized calcium level and will likely not have any symptoms. On the other hand, alkalosis will increase the binding affinity of albumin for calcium, causing a low ionized calcium but a normal total calcium.

C. Diagnosis

1. To evaluate for the above-listed etiologies, obtain the following: BUN, Cr, magnesium, albumin, and ionized calcium. Amylase, lipase, and

liver function tests may also be warranted.

2. Serum PO_4^{3-}: high in renal insufficiency and in hypoparathyroidism, low in primary vitamin D deficiency
3. PTH
   a. Low in hypoparathyroidism
   b. Elevated in vitamin D deficiency, CKD
   c. Very high in pseudohypoparathyroidism

D. Treatment

1. If symptomatic, provide emergency treatment with IV calcium gluconate.
2. For long-term management, use oral calcium supplements (calcium carbonate) and vitamin D.
3. For PTH deficiency.
   a. Replacement therapy with vitamin D (or calcitriol) plus a high oral calcium intake.
   b. Thiazide diuretics—lower urinary calcium and prevent urolithiasis.
4. It is also important to correct hypomagnesemia. It is very difficult to correct the calcium level if the magnesium is not replaced first.

Hypercalcemia

A. Causes

1. Endocrinopathies
   a. Hyperparathyroidism—increased Ca^{2+}, low PO_4^{3-}, usually due to an adenoma (most common cause in outpatients)
   b. Renal failure—usually results in hypocalcemia, but sometimes secondary hyperparathyroidism desensitizes the parathyroid to calcium levels and elevates PTH levels high enough to cause **hyper**calcemia (this is known as tertiary hyperparathyroidism)
   c. Paget disease of the bone—due to osteoclastic bone resorption
   d. Hyperparathyroidism, acromegaly, Addison disease
2. Malignancies (most common cause in inpatients)
   a. Metastatic cancer—bony metastases result in bone destruction due to osteoclastic activity. Most tumors that metastasize to bone cause

both osteolytic and osteoblastic activities (prostate cancer, mainly osteoblastic; breast and kidney carcinoma, usually osteolytic)

b. Multiple myeloma—secondary to two causes
   - Lysis of bone by tumor cells
   - Release of osteoclast-activating factor by myeloma cells

c. Tumors that release PTH-like hormone (e.g., squamous cell cancers such as lung, head, and neck)

d. Tumors that release PTH (lung, ovarian cancers)

e. Tumors that release vitamin D (e.g., lymphomas)

3. Pharmacologic
   a. Vitamin D intoxication—increased GI absorption of calcium
   b. Milk-alkali syndrome—hypercalcemia, alkalosis, and renal impairment due to excessive intake of calcium and certain absorbable antacids (calcium carbonate, milk)
   c. Drugs—thiazide diuretics (inhibit renal excretion), lithium (increases PTH levels in some patients, e.g., squamous cell carcinoma)
4. Other
   a. Sarcoidosis—increased GI absorption of calcium
   b. Familial hypocalciuric hypercalcemia—distinguished from primary hyperparathyroidism by a low urine calcium excretion versus a normal or high urine calcium excretion in primary hyperparathyroidism

B. Clinical Features

1. “Stones” (due to chronic hypercalciuria rather than hypercalcemia alone)
   a. Nephrolithiasis
   b. Nephrocalcinosis
2. “Bones”
   a. Bone aches and pains
   b. Osteitis fibrosa cystica (“brown tumors”) predisposes to pathologic fractures
3. “Grunts and groans”
   a. Muscle pain and weakness
   b. Pancreatitis
   c. Peptic ulcer disease

d. Gout
e. Constipation

4. "Psychiatric overtones"—depression, fatigue, anorexia, sleep disturbances, anxiety, lethargy
5. Other findings
   a. Polydipsia, polyuria
   b. Nephrogenic DI
   c. Hypertension
   d. Weight loss
   e. ECG—shortened QT interval
   f. Patients may be asymptomatic

Quick HIT

- In hypercalcemia, ECG shows shortening of the QT interval.
- In hypocalcemia, ECG shows a prolongation of the QT interval.

C. Diagnosis

1. Same laboratory tests as in hypocalcemia
2. Radioimmunoassay of PTH: elevated in primary hyperparathyroidism, low in occult malignancy
3. Radioimmunoassay of PTH-related protein: elevated in malignancy
4. Bone scan or bone survey to identify lytic lesions
5. Urinary cAMP: markedly elevated in primary hyperparathyroidism

D. Treatment

1. Patients usually do not require management beyond correction of underlying etiology unless hypercalcemia is severe (>14 mg/dL) or significant symptoms are present
2. Increase urinary excretion in all patients
   a. IV fluids (NS)—first step in management
   b. Diuretics (furosemide)—further inhibit calcium reabsorption, but should only be given in hypervolemic patients
3. Inhibit bone resorption in patients with osteoclastic disease (e.g., malignancy)
   a. Bisphosphonates (pamidronate)

   b. Calcitonin
4. Give glucocorticoids if vitamin D–related mechanisms (intoxication, granulomatous disorders) and multiple myeloma are the cause of the hypercalcemia. However, glucocorticoids are ineffective in most other forms of hypercalcemia
5. Use hemodialysis for renal failure patients
6. Phosphate is effective but incurs the risk of metastatic calcification

Potassium

Potassium Metabolism

- **Normal K^+ levels:** 3.5 to 5.0 mEq/L.
- **Location in the body**—most of the body's potassium (98%) is intracellular
- **Hypokalemia**—alkalosis and insulin administration may cause hypokalemia because they cause a shift of potassium into the cells
- **Hyperkalemia**—acidosis and anything resulting in cell lysis increase serum K^+ (both force K^+ out of cells into the ECF)
- **Potassium secretion**—most of the excretion of potassium occurs through the kidneys (80%); the remainder occurs via the GI tract. Aldosterone plays an important role in renal potassium secretion

Quick HIT

Serum potassium is affected by pH: alkalosis can lead to hypokalemia, whereas acidosis can lead to hyperkalemia.

Hypokalemia

A. Causes

1. GI losses
   a. Vomiting and nasogastric drainage (volume depletion and metabolic alkalosis also result)

b. Diarrhea
c. Laxatives and enemas
d. Intestinal fistulas—particularly after inflammatory bowel disorders such as Crohn's or diverticulitis
e. Decreased potassium absorption in intestinal disorders

2. Renal losses
a. Diuretics
b. Renal tubular or parenchymal disease
c. Primary and secondary hyperaldosteronism
d. Excessive glucocorticoids—due to mineralocorticoid action at high serum levels
e. Magnesium deficiency
f. Bartter syndrome—chronic volume depletion secondary to an autosomal-recessive defect in salt reabsorption in the thick ascending limb of the loop of Henle leads to hyperplasia of juxtaglomerular apparatus, which leads to increased renin levels and secondary aldosterone elevations.

3. Other causes
a. Insufficient dietary intake
b. Insulin administration
c. Certain antibiotics especially amphotericin B
d. Profuse sweating
e. Epinephrine (β_2-agonists)—hypokalemia occurs in 50% to 60% of trauma patients, perhaps due to increased epinephrine levels

Quick HIT

Diarrhea is a common cause of both hypokalemia and non-AG metabolic acidosis.

Quick HIT

The presence or absence of HTN is useful in differentiating the causes of hypokalemia. If the patient is hypertensive, excessive aldosterone activity is likely. If the patient is normotensive, either GI or renal loss of K^+ is likely.

Quick HIT

Always monitor K^+ levels in patients taking digoxin. It is common for these patients to be taking diuretics as well (for CHF), which can cause hypokalemia. **Hypokalemia predisposes the patient to digoxin toxicity.**

B. Clinical Features

1. **Arrhythmias**—prolongs normal cardiac conduction
   a. Exacerbates digitalis toxicity
   b. Flattening of T waves on ECG. U waves appear if severe
2. Muscular weakness, fatigue, paralysis, and muscle cramps
3. Decreased deep tendon reflexes
4. Paralytic ileus
5. Polyuria and polydipsia
6. Nausea/vomiting

Quick HIT

Arrhythmias are the most dangerous complications of hypokalemia. ECG changes in hypokalemia appear as follows:

- T wave flattens out; if severe, T wave inverts
- U wave appears

Quick HIT

Interpretation of urine potassium in hypokalemia

- Low with GI losses (<20 mEq/L)
- High with renal losses (>20 mEq/L)

C. Treatment

1. Identify and treat the underlying cause (Figure 8-4).
2. Discontinue any medications that can aggravate hypokalemia.
3. Oral KCl is the preferred (safest) method of replacement and is appropriate in most instances. Always retest the K^+ levels after administration.

a. Using 10 mEq of KCl usually increases K^+ levels by 0.1 mEq/L, it will increase levels more in patients with renal insufficiency due to decreased clearance.
b. It comes in slow-acting and fast-acting forms.

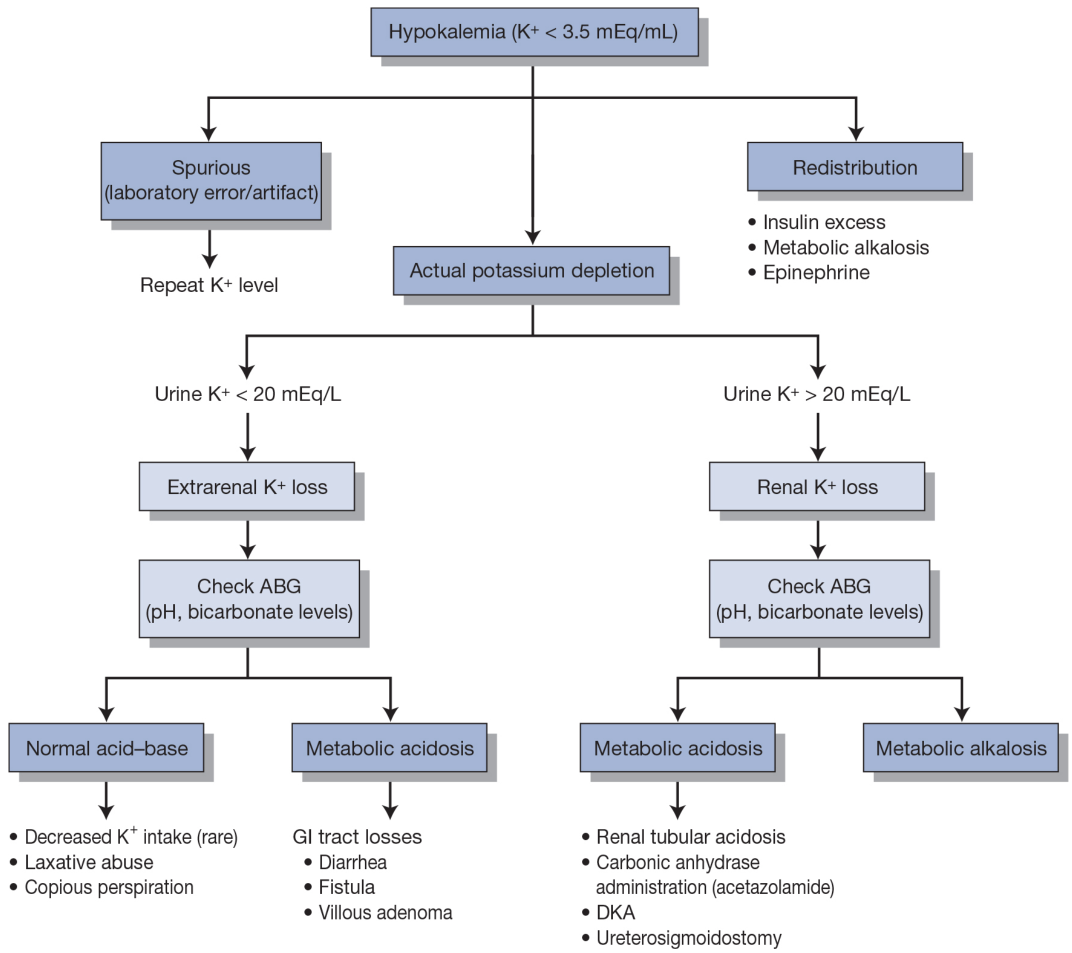


FIGURE 8-4 Diagnostic evaluation of hypokalemia.
(Adapted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:1165. Figure 146-2.)

4. IV KCl can be given if hypokalemia is severe (<2.5), if the patient cannot take PO, or if the patient has arrhythmias secondary to hypokalemia.
   a. Give slowly to avoid hyperkalemia.
   b. Monitor K^+ concentration and monitor cardiac rhythm when giving IV potassium.

c. Infusion pearls.
   - Maximum infusion rate of 10 mEq/hr in peripheral IV line.
   - Maximum infusion rate of 20 mEq/hr in central line.
   - May add 1% lidocaine to bag to decrease pain (potassium burns!).

5. As with calcium, it is difficult to correct the potassium level if any hypomagnesemia is not corrected first.

Hyperkalemia

A. Causes

1. Increased total-body potassium
   a. Renal failure (acute or chronic)
   b. Hypoaldosterone states: Addison disease, hyporeninemic hypoaldosteronism, ACE inhibitors, potassium-sparing diuretics (spironolactone)
   c. Iatrogenic—excessive doses of potassium (use caution when administering potassium in patients with renal failure) and certain medications (e.g., trimethoprim-sulfamethoxazole)
   d. Blood transfusion—usually due to lysed cells

Quick HIT

Hyperkalemia inhibits renal ammonia synthesis and reabsorption. Thus, net acid excretion is impaired and results in metabolic acidosis. This further exacerbates hyperkalemia due to K^+ movement out of cells.

2. Redistribution—translocation of potassium from intracellular to extracellular space
   a. Acidosis (notably not seen in lactic or ketoacidosis)
   b. Tissue/cell breakdown—rhabdomyolysis (muscle breakdown), chemotherapy, hemolysis, burns
   c. GI bleeding
   d. Insulin deficiency—insulin stimulates the Na^+–K^+–ATPase and causes K^+ to shift into cells. Therefore, insulin deficiency and hypertonicity (high glucose) promote K^+ shifts from ICF to ECF
   e. Rapid administration of β-blocker

3. Pseudohyperkalemia (spurious)
   a. This refers to an artificially elevated plasma K^+ concentration due to K^+ movement out of cells immediately before or after venipuncture. Contributing factors include **prolonged use of a tourniquet with or without repeated fist clenching.** This can cause acidosis and subsequent K^+ loss from cells. Nevertheless, plasma (not serum) K^+ should be normal. (Repeat the test to confirm this.)
   b. In addition, if the sample is not processed quickly, some red blood cells will hemolyze and cause spillage of K^+ leading to a falsely elevated result. The test should be repeated in this case.
   c. Other contributing factors include leukocytosis and thrombocytosis.

An older man is admitted to the hospital with weakness and palpitations, and found to have hyperkalemia. An ECG is performed and shows peaked T waves.

Which of the following is NOT a cause of this electrolyte abnormality?

A. Excessive insulin administration
B. Metabolic acidosis
C. Ischemic bowel
D. Excessive β-blocker administration
E. Excessive ACE inhibitor administration

- **The answer is A: Excessive insulin administration.** The classic ECG changes in hyperkalemia are peaked T waves, an increased PR interval, and an increased QRS width. If left untreated, the QRS complexes will progress to a sine wave pattern. All of the following will increase serum potassium concentrations: **(D, E)** anything that decreases the activity of the sodium–potassium ATPase (e.g., β-blockers, digoxin, ACE inhibitors/ARBs and hypoaldosteronism, insulin *deficiency*); **(B)** anything that causes acidemia and a transcellular shift of hydrogen ions into cells and potassium ions out of cells; **(C)** anything causing massive cell death/lysis (e.g., ischemic bowel, hemolysis, rhabdomyolysis, tumor lysis syndrome); and anything causing renal disease or a decrease in effective arterial volume (e.g., CHF, liver failure) that leads to the inability to excrete potassium. Also, be aware of pseudohyperkalemia, in which the laboratory sample that was drawn undergoes hemolysis and gives a falsely high serum potassium value.

B. Clinical Features

1. **Arrhythmias**—The most important effect of hyperkalemia is on the heart (Figure 8-5). Check an ECG immediately in a hyperkalemic patient. With increasing potassium, ECG changes progress through tall, peaked T waves, QRS widening, PR interval prolongation, loss of P waves, and finally a sine-wave pattern

2. Muscle weakness and (rarely) flaccid paralysis
3. Decreased deep tendon reflexes
4. Respiratory failure
5. Nausea/vomiting, intestinal colic, diarrhea
6. Acidosis due to decreased ammonium formation in renal tubules

Quick HIT

ECG changes in hyperkalemia become prominent when K^+ >6 and include:

- Peaked T waves (by 10 mm)
- A prolonged PR interval
- Widening of QRS and merging of QRS with T wave
- Ventricular fibrillation and cardiac arrest (with increasing levels of K^+)

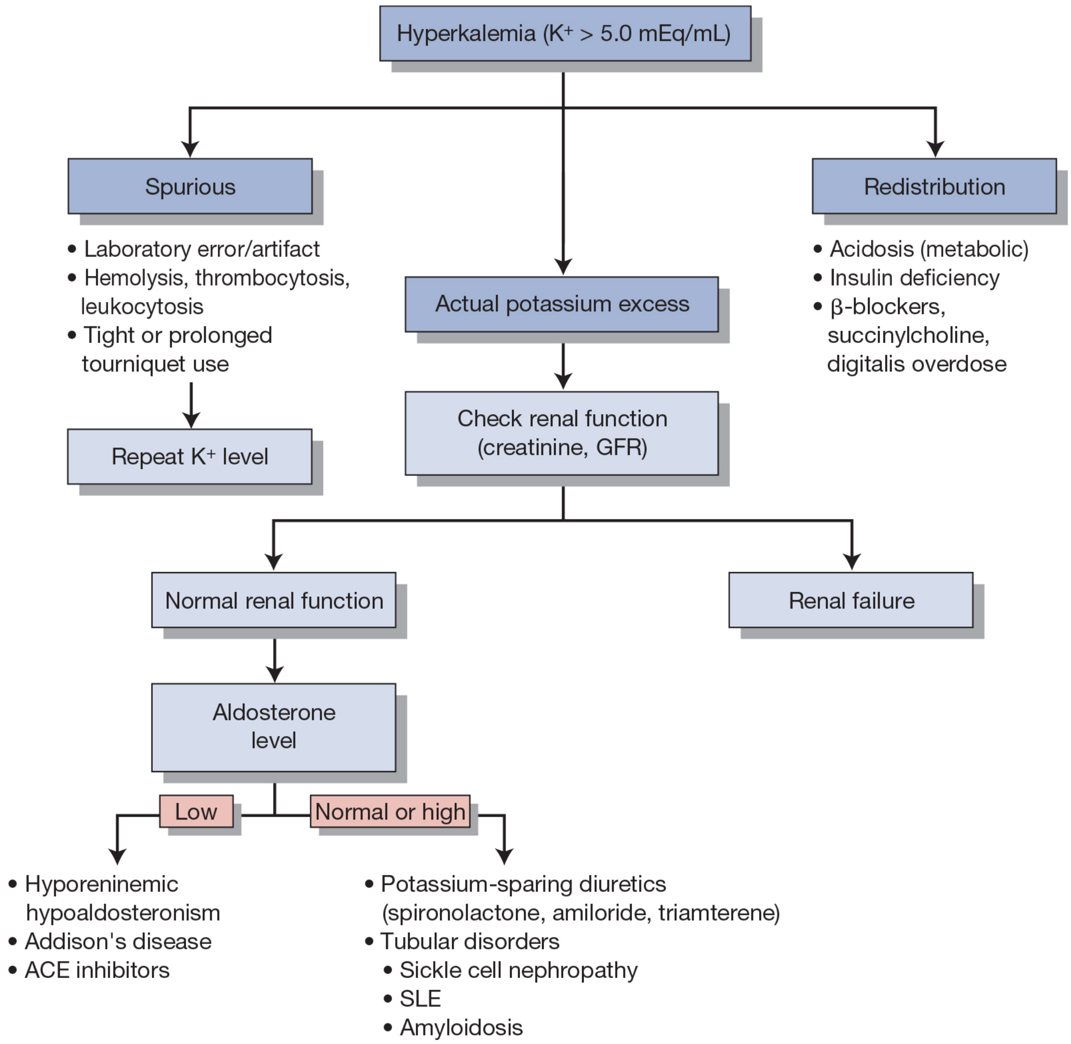


FIGURE 8-5 Diagnostic evaluation of hyperkalemia.
(Adapted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:1168. Figure 147-1.)

Quick HIT

Of all electrolyte disturbances, hyperkalemia is the most dangerous and can be the most rapidly fatal.

C. Treatment

1. If the hyperkalemia is severe, or if ECG changes are present, first give **IV calcium.**

a. Calcium stabilizes the resting membrane potential of the myocardial membrane—that is, it decreases membrane excitability.
b. Use caution in giving calcium to patients on digoxin. (Hypercalcemia predisposes the patient to digoxin toxicity.)

2. Shift potassium into the intracellular compartment.
   a. **Glucose and insulin**—Works via stimulation of Na^+/K^+ pump. Glucose alone will stimulate insulin from β-cells, but exogenous insulin is more rapid (and thus should be one of the first steps in management). Give both to prevent hypoglycemia.
   b. β-Agonists (e.g., albuterol)—Also works via stimulation of Na^+/K^+ pump. Transient management in those with symptoms or ECG changes.
   c. Sodium bicarbonate—Increases pH level, which shifts K^+ into cells via H^+/K^+ pump. Similar to β-agonists, an emergency measure in severe hyperkalemia.
3. Remove potassium from the body.
   a. Diuretics (e.g., furosemide)
   b. GI cation exchangers: newer agents patiromer or sodium zirconium cyclosilicate are now preferred to kayexalate (sodium polystyrene sulfonate) if available. These help to bind and remove potassium in the GI tract. Hemodialysis.
      - Most rapid and effective way of lowering plasma K^+.
      - Reserved for intractable hyperkalemia (usually over 7) and for those with renal failure.

Magnesium

Overview

- **Normal Mg^{2+} levels:** 1.8 to 2.5 mg/dL.
- **Location in the body**—Most of the magnesium in the body (two-thirds) is in bones. The remainder (one-third) is intracellular. Only 1% of magnesium is extracellular.
- **Influences on magnesium excretion**—Many hormones can alter urinary magnesium excretion (e.g., insulin/glucagons, PTH, calcitonin, ADH, and

steroids).

- **Magnesium absorption and balance**—About 30% to 40% of dietary magnesium is absorbed in the GI tract, but this percentage increases when magnesium levels are low. The kidney has a great capacity to reabsorb magnesium and is the major regulator of magnesium balance.

Hypomagnesemia

A. Causes

1. GI causes
   a. Malabsorption, steatorrheic states (most common cause)
   b. Prolonged fasting
   c. Fistulas
   d. Patients receiving TPN without Mg^{2+} supplementation

> **Quick HIT**
>
> Hypomagnesemia makes hypokalemia and hypocalcemia more difficult to treat.

2. Alcoholism (common cause)—due to increased urinary excretion as well as frequently concomitant diarrhea, pancreatitis, and poor diet
3. Renal causes
   a. SIADH
   b. Diuretics (often seen in patients being treated for heart failure exacerbation)
   c. Gitelman and Bartter syndromes
   d. Drugs: gentamicin, amphotericin B, cisplatin
   e. Renal transplantation
4. Other causes: postparathyroidectomy, DKA, thyrotoxicosis, lactation, burns, pancreatitis, cisplatin

B. Clinical Features

1. Marked neuromuscular and CNS hyperirritability
   a. Muscle twitching, weakness, tremors

b. Hyperreflexia, seizures
c. Mental status changes
2. Effect on calcium levels: **coexisting hypocalcemia is common** because of decreased release of PTH and bone resistance to PTH when Mg^{2+} is low
3. Effect on potassium levels
a. **Coexisting hypokalemia**—in up to 50% of cases, usually due to etiology which leads to loss of both
b. In muscle and myocardium, when either intracellular Mg^{2+} or K^+ decreases, a corresponding decrease in the other cation takes place
4. ECG changes—prolonged QT interval, T-wave flattening, and ultimately, torsade de pointes

C. Treatment

1. For mild hypomagnesemia—oral Mg^{2+} (e.g., magnesium oxide)
2. For severe hypomagnesemia—parenteral Mg^{2+} (e.g., magnesium sulfate)

Hypermagnesemia

A. Causes

1. Renal failure (most common cause)
2. Early-stage burns, massive trauma or surgical stress, severe ECF volume deficit, severe acidosis
3. Excessive intake of magnesium-containing laxatives or antacids combined with renal insufficiency
4. Adrenal insufficiency
5. Rhabdomyolysis
6. Iatrogenic—usually in the obstetric setting in women with preeclampsia or eclampsia being treated with magnesium sulfate

B. Clinical Features

1. Nausea, weakness
2. Facial paresthesias
3. Progressive loss of deep tendon reflexes (classically the first sign)

4. ECG changes resemble those seen with hyperkalemia (increased PR interval, widened QRS complex, and elevated T waves)
5. Somnolence leading to coma and muscular paralysis occur late
6. Death is usually caused by respiratory failure or cardiac arrest

> ***Quick* HIT**
>
> Hyperkalemia and hypermagnesemia have some similar etiologies, cause suppression of muscular function, and induce similar ECG changes, so always check magnesium when suspecting hyperkalemia!

C. Treatment

1. Withhold exogenously administered magnesium.
2. Prescribe IV calcium gluconate for emergent symptoms (cardioprotection as in hyperkalemia).
3. Administer saline and furosemide.
4. Order dialysis in renal failure patients.
5. Prepare to intubate if respiratory depression is severe.

Phosphate

Overview

- Normal phosphate levels: 3.0 to 4.5 mg/dL.
- Location in the body—Most of the phosphorus is in the bones (85%); the remainder is intracellular in soft tissues (15%) and a very small amount (0.1%) in ECF
- Influence on phosphate absorption—Vitamin D controls phosphorus absorption in the GI tract
- Phosphate excretion and balance—PTH controls phosphorus excretion in the kidney—PTH increases renal phosphorus excretion by inhibiting reabsorption. The function of the kidney in maintaining phosphate balance is very important

Quick HIT

Plasma Phosphate Concentration

- Normal: 3.0 to 4.5 mg/dL
- **Hypo**phosphatemia: <2.5 mg/dL
- **Hyper**phosphatemia: >5 mg/dL

Hypophosphatemia

A. Causes

1. Decreased intestinal absorption due to alcohol abuse, vitamin D deficiency, malabsorption of phosphate, excessive use of phosphate-binding antacids, hyperalimentation (TPN), and/or starvation
2. Increased renal excretion
   a. Excess PTH states (vitamin D deficiency, hyperparathyroidism)
   b. Hyperglycemia (glycosuria), oncogenic osteomalacia, ATN, renal tubular acidosis, and so on
   c. Hypokalemia or hypomagnesemia
3. Other causes: respiratory alkalosis, anabolic steroids, severe hyperthermia, DKA, hungry bone syndrome (deposition of bone material after parathyroidectomy)

Quick HIT

The most common causes of severe hypophosphatemia are alcohol abuse and DKA.

B. Clinical Features

1. None, if the hypophosphatemia is mild.
2. Any of the following, if the hypophosphatemia is severe, primarily due to a lack of available ATP and 2,3 DPG, the latter causing decreased O_2 release from RBC:
   a. Neurologic: encephalopathy, confusion, seizures, numbness, paresthesias

b. Musculoskeletal: muscular weakness, myalgias, bone pain, rickets/osteomalacia
c. Hematologic: hemolysis, RBC dysfunction, WBC dysfunction, platelet dysfunction
d. Cardiac: cardiomyopathy and myocardial depression secondary to low ATP levels, may lead to cardiac arrest
e. Rhabdomyolysis
f. Anorexia
g. Difficulty in ventilator weaning

C. Treatment

1. If mild (>1 mg/dL), oral supplementation: Neutra-Phos capsules, K-Phos tablets, milk (excellent source of phosphate)
2. If severe/symptomatic or if patient is NPO: parenteral supplementation

Hyperphosphatemia

A. Causes

1. Decreased renal excretion of PO_4^{3-} due to renal insufficiency (most common cause), bisphosphonates, hypoparathyroidism, vitamin D intoxication, and/or tumor calcinosis
2. Increased phosphate administration (e.g., PO_4^{3-} repletion or PO_4^{3-} enemas)
3. Rhabdomyolysis, cell lysis, or acidosis (releases PO_4^{3-} into the ECF)

B. Clinical Features

1. This results in metastatic calcification and soft tissue calcifications; a calcium-phosphorus product (serum calcium × serum phosphorus) >**70** indicates that calcification is likely to occur. A calcium-phosphate product <**55** is usually the goal for CKD patients to prevent calcification.
2. The associated hypocalcemia can lead to neurologic changes (tetany, neuromuscular irritability).

C. Treatment

1. Phosphate-binding antacids containing aluminum hydroxide or carbonate (bind phosphate in bowel and prevent its absorption)
2. Hemodialysis (if patient has renal failure)

Acid–Base Disorders

Metabolic Acidosis

A. General Characteristics

1. Metabolic acidosis is characterized by decreased blood pH and a decreased plasma bicarbonate concentration (see Clinical Pearl 8-2). The goal is to identify the underlying condition that is causing the metabolic acidosis.

CLINICAL PEARL 8-2

Effects of Acidosis and Alkalosis

- **Acidosis**
  - Right shift in oxygen–hemoglobin dissociation curve diminishes the affinity of hemoglobin for oxygen (so increases oxygen delivery to tissues)
  - Depresses CNS
  - Decreases pulmonary blood flow
  - Arrhythmias
  - Impairs myocardial function
  - Hyperkalemia
- **Alkalosis**
  - Decreases cerebral blood flow
  - Left shift in oxygen–hemoglobin dissociation curve increases the affinity of hemoglobin for oxygen (so decreases oxygen delivery to tissues)
  - Arrhythmias
  - Tetany, seizures

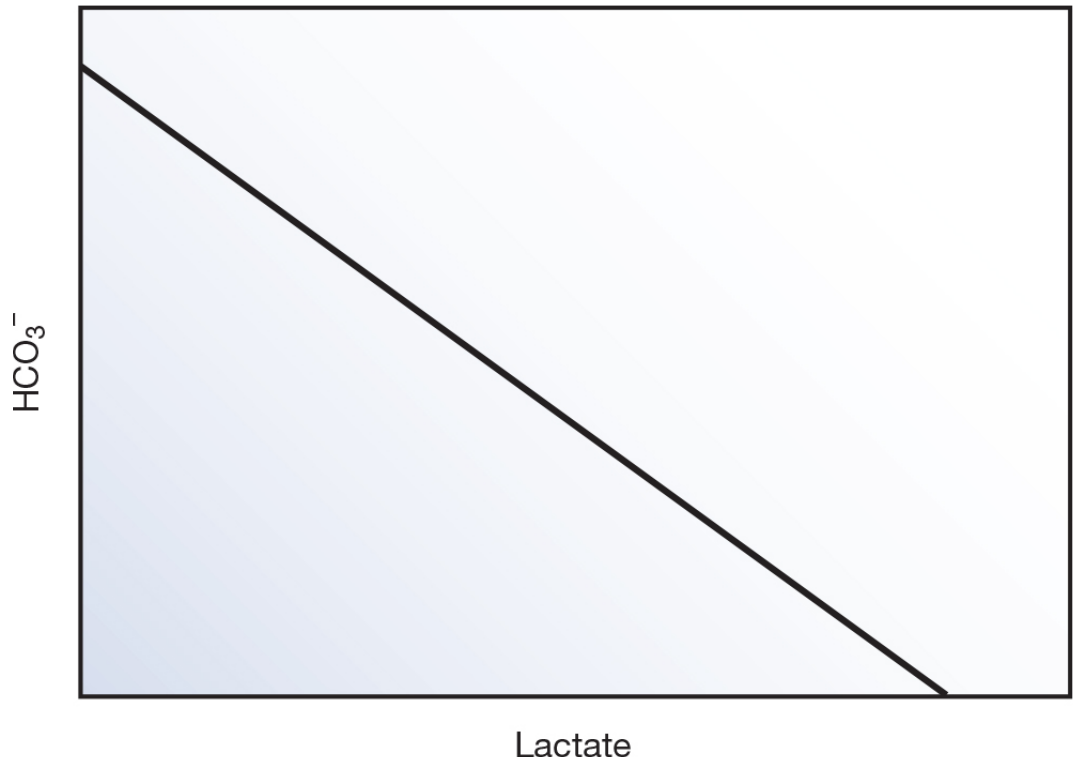


FIGURE 8-6 **An increase in lactate results in a decrease in HCO_3^- (due to buffering) in ECF. The kidneys must then reabsorb more HCO_3^- to maintain pH.**

2. Anion gap (AG)—A useful measurement for identifying the cause of acidosis, whether due to a relative excess of chloride with respect to bicarbonate (normal gap) or an abundance of other acids (high gap)
   a. AG (mEq/L) = $[Na^+] - ([Cl^-] + [HCO_3^-])$
   b. Reflects ions present in serum but unmeasured (i.e., proteins, phosphates, organic acids, sulfates)
   c. Normal values are 5 to 15 mEq/L, but this varies to some extent
   d. Always check albumin level and add 2.5 to gap for every 1 g/dL below 4
3. Pathophysiology (Figure 8-6).
   a. Anion gap metabolic acidosis: When a fixed acid (lactic acid, ketones, salicylic acid) is added, the H^+ is buffered by the bicarbonate system. CO_2 is formed and removed by lungs (respiratory compensation). $H^+ + HCO_3^- \leftrightarrow H_2CO3^- \leftrightarrow H_2O + CO_2$. HCO_3^- levels decrease in ECF and the conjugate bases of the acid in

the serum now exist as unmeasured anions which raise the measured gap. With time, kidneys reabsorb more HCO_3^- (new) to maintain pH (renal compensation).

b. Nonanion gap metabolic acidosis: Bicarbonate is lost without being used as a buffer to an added acid, usually in GI tract or urine, or chloride concentration relatively increases.

c. Three situations can arise:

- The change in AG equals the change in HCO_3^- (see Figure 8-7A): simple metabolic acidosis—the addition of acid causes the AG to increase proportionally.
- The change in AG is less than the change in HCO_3^- (see Figure 8-7B): **normal AG acidosis PLUS high AG acidosis**—If after the addition of acid, the HCO_3^- is lower than the calculated prediction, then you started with a lower HCO_3^-.
- The change in AG is greater than the change in HCO_3^- (see Figure 8-7C): **metabolic alkalosis PLUS high AG acidosis**—when you have a high AG, the acid has to be buffered by HCO_3^-, so HCO_3^- decreases. If HCO_3^- does not decrease, it means you started at a higher HCO_3^-.

***Quick* HIT**

The bicarbonate level obtained in a serum chemistry panel (venous CO_2) is a measured value (more reliable), whereas the level obtained in an arterial blood gas is a calculated value (less reliable).

B. Causes

1. Increased AG acidosis (see also Clinical Pearl 8-3)

a. Ketoacidosis

- Diabetes mellitus
- Prolonged starvation
- Prolonged alcohol abuse

b. Lactic acidosis—can occur in many different conditions

- Low tissue perfusion (decreased oxygen delivery to tissues)
- Shock states (septic, cardiogenic, hypovolemic)

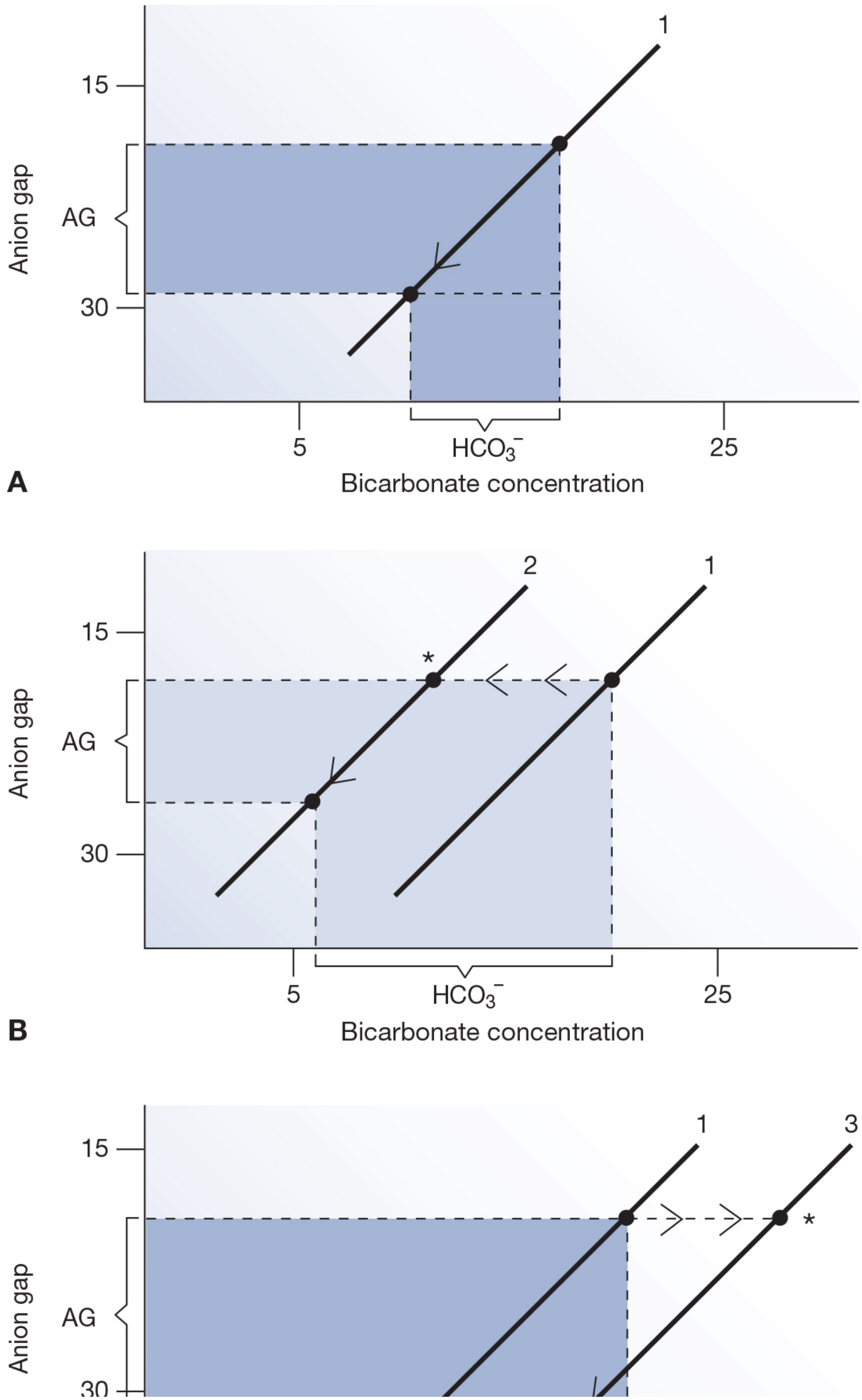
- Excessive expenditure of energy (e.g., seizures)

c. Renal failure—decreased NH_4^+ excretion (thus decreasing net acid)—decreased excretion of organic anions, sulfate, and phosphate increases AG

d. Intoxication
- Salicylate (aspirin)
- Methanol
- Ethylene glycol

Quick HIT

Salicylate overdose causes both primary respiratory alkalosis **and** primary metabolic acidosis.



1
15
AG
30
Anion gap
5
HCO_3^-
25
A
Bicarbonate concentration
2
1
*
15
AG
30
Anion gap
5
HCO_3^-
25
B
Bicarbonate concentration
1
3
*
15
AG
30
Anion gap

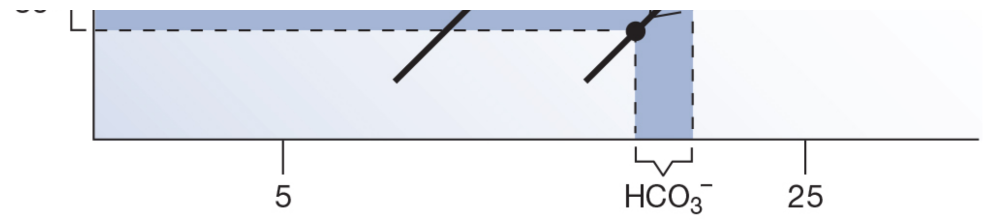


FIGURE 8-7 **A: Simple metabolic acidosis. The change in AG is equal to the change in HCO_3^-. As you add acid, HCO_3^- decreases, and AG increases proportionately. B: Normal anion gap acidosis PLUS high anion gap acidosis. The change in AG is less than the change in HCO_3^-. If after the addition of acid, HCO_3^- is lower than predicted, then you started at a lower HCO_3^- level (*). C: Metabolic alkalosis plus high anion gap acidosis. The change in AG is greater than the change in HCO_3^-. If after the addition of acid, the *decrease* in HCO_3^- is less than expected, then you started at a higher HCO_3^- level (*).**

2. Normal AG acidosis (hyperchloremic metabolic acidosis)—The low HCO_3^- is associated with high Cl^-, so that the AG remains normal
   a. Renal loss of bicarbonate
      - Proximal tubular acidosis—this is characterized by decreased HCO_3^- reabsorption. Causes include multiple myeloma, cystinosis, and Wilson disease.
      - Distal tubular acidosis—this is characterized by the inability to make HCO_3^-. Causes include SLE, Sjögren syndrome, and taking amphotericin B.
      - Carbonic anhydrase inhibition (e.g., acetazolamide—a diuretic)

   b. GI loss of HCO_3^-
      - Diarrhea—HCO_3^- loss in diarrhea **(most common cause of non-AG acidosis)**
      - Pancreatic fistulas—pancreatic secretions contain high HCO_3^- levels
      - Small bowel fistulas
      - Ureterosigmoidostomy—colon secretes HCO_3^- in urine in exchange for Cl^-

   c. Insufficient excretion of daily acid load

    - Hypoaldosterone states: Addison disease, spironolactone, amiloride, triamterene
    - CKD
  d. Chloride excess
    - Primarily due to iatrogenic saline infusions

CLINICAL PEARL 8-3

Arterial Blood Gas Interpretation

- **CO_2 level**
  - If elevated, think of either respiratory acidosis or compensation for metabolic alkalosis.
  - If low, think of either respiratory alkalosis or compensation for metabolic acidosis.
- **HCO_3^- level**
  - If elevated, think of either metabolic alkalosis or compensation for respiratory acidosis.
  - If low, think of either metabolic acidosis or compensation for respiratory alkalosis.
  - The base excess/base deficit values in the arterial blood gas indicate the amount of acid or base that is needed to titrate the plasma pH to 7.40 (with a $PaCO_2$s of 40).

C. Clinical Features

1. Hyperventilation (deep rhythmic breathing), also known as Kussmaul respiration
   a. This is a typical compensation (i.e., response) for a metabolic acidosis and is a cardinal feature of metabolic acidosis; it is usually seen in severe metabolic acidosis (pH <7.20).
   b. It is less prominent when the acidosis is chronic.
2. Decreased cardiac output and decreased tissue perfusion
   a. Occurs with severe metabolic acidosis (blood pH <7.2).
   b. Acidosis diminishes tissue responsiveness to catecholamines. This can lead to an undesirable chain of events: poor tissue perfusion → lactic acidosis → decreased cardiac output → hypotension → further decrease in tissue perfusion.

D. Diagnosis

1. History is important.
2. Calculate the AG.
3. If gap is present, calculate the Delta Gap = (measured anion gap − 12) + HCO_3^-
   a. Delta gap > 26 ± 2: Concurrent metabolic alkalosis
   b. Delta gap < 20 ± 2: Concurrent nonanion gap metabolic acidosis
4. If no gap is present, urine anion gap can be measured ($U_{Na}^+ + U_K^+ - U_{Cl}^-$)
   a. If positive, suggests low urinary NH_4^+ (renal etiology of acidosis due to inability of renal tubules to excrete acid, likely RTA)
   b. If negative, suggests appropriate urinary NH_4^+ (nonrenal cause of acidosis)
5. Calculate Winter formula: **expected $PaCO_2$** = 1.5 (measured HCO_3^-) + 8 ± 2.
   a. Predicts the expected respiratory compensation ($PaCO_2$ level) to metabolic acidosis: If the $PaCO_2$ does not fall within an acceptable range, then the patient has a respiratory acid–base disorder as well.
   b. If the $PaCO_2$ falls within the predicted range, then the patient has a simple metabolic acidosis with an appropriate secondary hypocapnia.
   c. If the actual $PaCO_2$ is higher than the calculated $PaCO_2$, then the patient has metabolic acidosis with respiratory acidosis (i.e., they are underbreathing). **This is a serious finding because this failure of compensation can be a sign of impending respiratory failure. The classic example is an asthmatic child who has a $PaCO_2$ that goes from abnormal to normal with no treatment. This is a bad sign, and it probably means the child will need emergent intubation shortly.**
   d. If the actual $PaCO_2$ is lower than the calculated $PaCO_2$, then the patient has metabolic acidosis with respiratory alkalosis (i.e., they are overbreathing).

Quick HIT

With metabolic **acidosis,** $PaCO_2$ should decrease. With metabolic **alkalosis,** $PaCO_2$ should increase. This is normal respiratory compensation. **Failure of respiratory compensation indicates an additional primary respiratory acid–base disorder.**

E. Treatment

1. Treatment varies depending on the cause.
2. Sodium bicarbonate is sometimes needed (especially for normal AG acidosis and with renal dysfunction) in severe acidosis to maintain a pH of no lower than 7.20. In correcting metabolic acidosis, realize that this HCO_3^- takes 24 hours to get to the brain. During this time, hyperventilation continues. Therefore, $PaCO_2$ remains low while HCO_3^- is increasing—a dangerous combination ($[H^+] = 24\ [PaCO_2 \div HCO_3^-]$).
3. Mechanical ventilation may be required if the patient is fatigued from prolonged hyperventilation, especially in DKA.

A 69-year-old man presents to the physician for fatigue and bone pain. His workup shows that he is anemic with the presence of an M-protein in the serum and urine, and he is diagnosed with multiple myeloma. Some of his other laboratory values are shown below.

Sodium	140 mEq/L
Potassium	3.2 mEq/L
Chloride	114 mEq/L
Bicarbonate	16 mEq/L
Phosphorus	1.9 mg/dL

An arterial blood gas shows that he has a pH of 7.3 and a $PaCO_2$ of 35 mmHg. Urine studies are significant for glucosuria, a urine pH of 7.8 after bicarbonate infusion, and a fractional excretion of bicarbonate of 25%.

Which of the following best represents the acid–base abnormality in this patient?

A. Anion gap metabolic acidosis with a compensatory respiratory alkalosis
B. Nonanion gap metabolic acidosis with a compensatory respiratory alkalosis
C. Anion gap metabolic acidosis with a primary respiratory acidosis
D. Nonanion gap metabolic acidosis with a primary respiratory acidosis

- **The answer is B: Nonanion gap metabolic acidosis with a compensatory respiratory alkalosis.** In this case, the reader can get the answer without even knowing that the diagnosis of multiple myeloma and proximal (type 2) renal tubular acidosis (presenting with the Fanconi syndrome, which is a syndrome of proximal tubule dysfunction with a decrease in the reabsorption of bicarbonate, phosphate, amino acids, and glucose). **(A, C)** From the laboratory values, the calculated anion gap is 10, ruling out an anion gap metabolic acidosis. The pH, bicarbonate, and $PaCO_2$ are all low,

indicating a metabolic acidosis. To compensate, patients will increase their ventilation to decrease the amount of CO_2 in the blood, producing a compensatory respiratory alkalosis. To determine if the respiratory compensation is appropriate, Winter formula can be used: $PaCO_2 = (1.5 \times HCO_3) + 8 \pm 2$. **(D)** In the case above, the $PaCO_2$ should be 30 to 36 mmHg, which fits with the actual value of 35 mmHg confirming that the compensation is appropriate. If the patient were overcompensating (e.g., $PaCO_2$ 28 mmHg), then a primary respiratory alkalosis would be present; if undercompensating (e.g., $PaCO_2$ 38 mmHg), then a primary respiratory acidosis would be present.

Quick HIT

While evaluating a patient with metabolic alkalosis, the first step is to determine whether the ECF volume has contracted or expanded, and why.

Metabolic Alkalosis

A. General Characteristics

1. Metabolic alkalosis is characterized by an increased blood pH and plasma HCO_3^-
2. Uncomplicated metabolic alkalosis is typically transient, because kidneys can normally excrete the excess HCO_3^-
3. Consider two events in metabolic alkalosis:
   a. Event that initiates the metabolic alkalosis (loss of H^+ via gastric drainage, vomiting, and so on), or increased HCO_3^- concentration due to ECF volume contraction
   b. Mechanism that **maintains** the metabolic alkalosis due to the kidney's inability to excrete the excess HCO_3^-

B. Causes

1. Saline-sensitive metabolic alkalosis (urine chloride <10 mEq/L)—characterized by **ECF contraction** and hypokalemia, usually due to HCO_3^- loss and/or RAAS system activation.
   a. Vomiting or nasogastric suction—When the patient loses HCl, gastric HCO_3^- generation occurs, which causes alkalosis.
   b. Diuretics—These decrease the ECF volume. Body HCO_3^- content remains normal, but plasma HCO_3^- increases because of ECF contraction.
   c. Villous adenoma of colon, diarrhea with high chloride content.
2. Saline-resistant metabolic alkalosis (urine chloride >20 mEq/L)—characterized by **ECF expansion** and hypertension (due to increased mineralocorticoids).
   a. Most are secondary to adrenal disorders (primary hyperaldosteronism). Increased levels of mineralocorticoid secretion lead to increased tubular reabsorption of Na^+ and HCO_3^-, and an excessive loss of Cl^-, K^+, and H^+ in the urine. The result is metabolic alkalosis and expansion of the ECF compartment (because of increased Na^+ reabsorption).
   b. Other causes include Cushing syndrome, severe K^+ deficiency, Bartter syndrome, and diuretic abuse.

Quick **HIT**

Exogenous bicarbonate loading (administering bicarbonate) can cause metabolic alkalosis, but this usually occurs in ESRD.

Quick **HIT**

It is useful to distinguish between the following:

- Metabolic alkalosis with volume **contraction** (usually due to fluid loss—e.g., vomiting or diuretics)
- Metabolic alkalosis with volume **expansion** (usually due to pathology of adrenal gland). An easy way to make this distinction is via the chloride concentration in the urine.

C. Clinical Features

1. There are no characteristic signs or symptoms.
2. The patient's medical history is most helpful (look for vomiting, gastric drainage, diuretic therapy, and so on).

D. Diagnosis

1. Elevated HCO_3^- level, elevated blood pH.
2. Hypokalemia is common (due to renal loss of K1).
3. $PaCO_2$ is elevated as a compensatory mechanism (due to hypoventilation). It is rare for a compensatory increase in $PaCO_2$ to exceed 50 to 55 mmHg (the respiratory rate to achieve this is so low that PaO_2 would be decreased). A higher value implies a superimposed respiratory acidosis.
4. The urine chloride level is very important in distinguishing between saline-sensitive and saline-resistant types.

E. Treatment

1. Treat the underlying disorder that caused the metabolic alkalosis.
2. NS plus potassium will restore the ECF volume if the patient is volume contracted.
3. Address the underlying cause (or prescribe spironolactone) if the patient is volume expanded.

Quick HIT

Any disorder that reduces CO_2 clearance (i.e., inhibits adequate ventilation) can lead to respiratory acidosis.

Respiratory Acidosis

A. General Characteristics

1. Defined as a reduced blood pH and $PaCO_2$ >40 mmHg.
2. Renal compensation (increased reabsorption of HCO_3^-) begins within 12 to 24 hours and takes 5 days or so to complete.

B. Causes—alveolar hypoventilation

1. Primary pulmonary diseases—for example, COPD, airway obstruction
2. Neuromuscular diseases—for example, myasthenia gravis
3. CNS malfunction—injury to brainstem
4. Drug-induced hypoventilation (e.g., from morphine, anesthetics, or sedatives)—narcotic overdose in postoperative patients is a possibility (look for pinpoint pupils).
5. Respiratory muscle fatigue

Quick HIT

Increased $PaCO_2$, → increased cerebral blood flow, → increased CSF pressure, which results in generalized CNS depression.

C. Clinical Features

1. Somnolence, confusion, and myoclonus with asterixis.
2. Headaches, confusion, and papilledema are signs of acute CO_2 retention.

D. Diagnosis

1. Elevation of HCO_3^-, $PaCO_2$
2. Determine if acute or chronic acidosis. Clinical history is important, though it can also be calculated; for every 10 mmHg increase in $PaCO_2$, pH will decrease roughly:
   a. 0.07 in acute acidosis
   b. 0.03 in chronic acidosis
   c. Intermediate values suggest a mixed picture
3. Calculate if renal compensation is appropriate:
   a. Acute respiratory acidosis
      - There is an immediate compensatory elevation of HCO_3^-.
      - There is an increase of 1 mmol/L for every 10 mmHg increase in $PaCO_2$.

   b. Chronic respiratory acidosis

- Renal adaptation occurs, and HCO_3^- increases by 3 to 4 mmol/L for every 10 mmHg increase in $PaCO_2$.
- This is generally seen in patients with underlying lung disease, such as chronic obstructive pulmonary disease (COPD).

E. Treatment

1. Verify patency of the airway.
2. If PaO_2 is low (<60 mmHg), initiate supplemental oxygen. **Caution:** In patients who are "CO_2 retainers" (e.g., COPD patients), oxygen can exacerbate the respiratory acidosis, so administer oxygen judiciously. (See the discussion under Acute Respiratory Failure in Chapter 2.)
3. Correct reversible causes.
4. Any measure to improve alveolar ventilation.
   a. Aggressive pulmonary toilet.
   b. Correct reversible pulmonary disease (e.g., treat pneumonia).
   c. Remove obstruction.
   d. If there is drug-induced hypoventilation, clear the agent from the body (**naloxone**!).
   e. Administer bronchodilators.
5. Intubation and mechanical ventilation may be necessary to relieve the acidemia and hypoxia that result from hypoventilation. The following situations require intubation:
   a. Severe acidosis.
   b. $PaCO_2$ >60 or inability to increase PaO_2 with supplemental oxygen.
   c. If patient is obtunded or shows deterioration in mental status.
   d. Impending respiratory fatigue (ensues with prolonged labored breathing).

A 62-year-old woman with a long history of COPD presents to her physician for routine laboratory tests. She is currently healthy without any recent illnesses or changes in medications. Her laboratory values show a serum bicarbonate level of 36 mEq/L.

Which of the following best represents the natural compensatory response to this patient's acid–base disorder?

A. Increased reabsorption of HCO_3 in the nephron
B. Decreased reabsorption of HCO_3 in the nephron
C. Increased respiratory rate and/or tidal volume
D. Decreased respiratory rate and/or tidal volume
E. Increased HCO_3 absorption in the GI tract

- **The answer is A: Increased reabsorption of HCO_3 in the nephron.** An elevated HCO_3 is consistent with either a metabolic alkalosis or a respiratory acidosis. In this case, the presence of a chronic lung disease such as COPD makes the likely diagnosis chronic respiratory acidosis. For chronic respiratory acidosis, the compensation will be an increase in HCO_3 reabsorption in the nephron (as well as an increase in the excretion of titratable acid and NH_4^+). **(B)** Chronic respiratory alkalosis will have the opposite effect, with a decrease in HCO_3 reabsorption. **(C, D)** In response to metabolic acidosis, the body will increase ventilation (respiratory rate × tidal volume); in response to metabolic alkalosis, the body will decrease ventilation. If a metabolic acidosis persists, the body's kidneys will also increase the excretion of titratable acid and NH_4^+. **(E)** The GI tract is not a major contributor to acid–base homeostasis.

Respiratory Alkalosis

A. General Characteristics

1. Characterized by an increased blood pH and decreased $PaCO_2$.
2. Chronicity of disease can, as in respiratory acidosis, be determined by clinical history or estimated through change in pH. For every 10 mmHg decrease in $PaCO_2$, pH will increase roughly:
   a. 0.07 in acute alkalosis
   b. 0.03 in chronic alkalosis
3. In order to maintain blood pH within the normal range, HCO_3 must decrease, so renal compensation occurs (i.e., HCO_3^- excretion increases). However, this does not occur acutely, but rather over the course of several hours.
   a. Acutely, for each 10 mmHg decrease in $PaCO_2$, plasma HCO_3^- decreases by 2 mEq/L and blood pH increases by 0.08 mEq/L.
   b. Chronically, for each 10 mmHg decrease in $PaCO_2$, plasma HCO_3^- decreases by 5 to 6 mEq/L and blood pH decreases by 0.02 mEq/L.

Quick HIT

$PaCO_2$ is primarily determined by respiratory rate and tidal volume.

B. Causes—alveolar hyperventilation

1. Anxiety
2. Pulmonary embolism, pneumonia, asthma
3. Sepsis
4. Hypoxia—leads to increased respiratory rate
5. Mechanical ventilation
6. Pregnancy—increased serum progesterone levels cause hyperventilation
7. Liver disease (cirrhosis)
8. Medication (salicylate toxicity)
9. Hyperventilation syndrome

Quick HIT

Any disorder that increases the respiratory rate inappropriately can lead to respiratory alkalosis.

C. Clinical Features

1. Symptoms are mostly related to decreased cerebral blood flow (vasoconstriction): lightheadedness, dizziness, anxiety, paresthesias, and perioral numbness
2. Tetany (indistinguishable from hypocalcemia)
3. Arrhythmias (in severe cases)

D. Treatment

1. Correct the underlying cause.
2. Sometimes this does not need to be treated (e.g., in the case of pregnancy).
3. An inhaled mixture containing CO_2 or breathing into a paper bag may be useful.

Hematologic Diseases and Neoplasms 9

Kelley Chuang

Anemias

Basics of Anemia

A. General Characteristics

1. Anemia is defined as a reduction in the number of circulating red blood cells, as measured by hemoglobin (Hb) or hematocrit (Hct)
2. When red cell mass decreases, several compensatory mechanisms maintain oxygen delivery to the tissues, including:
   a. Increased cardiac output
   b. Increased oxygen extraction ratio
   c. Rightward shift of the oxyhemoglobin curve (increased 2,3-diphosphoglycerate [2,3-DPG])
   d. Expansion of plasma volume

Quick HIT

Historical Findings to Consider in Patients With Anemia

- Family history (e.g., hemophilia, G6PD deficiency, thalassemia)
- Bleeding (e.g., recent trauma/procedure, hematemesis, melena)
- Chronic illnesses (e.g., renal failure, autoimmune diseases, malignancies)
- Ingestions (e.g., alcohol, medications)

3. Symptoms of anemia are highly variable, depending on the severity of anemia, the rate at which it developed, and the underlying oxygen

demands of the patient. If anemia develops rapidly, symptoms are more likely to be present, because there is little time for physiologic compensation. If the onset is gradual, compensatory mechanisms are able to maintain adequate oxygen delivery to tissues, and symptoms may be minimal or absent

4. As a general rule, blood transfusion is not recommended unless either of the following is true:
   a. The Hb concentration is <7 g/dL *OR*
   b. The patient requires increased oxygen-carrying capacity (e.g., patients with active coronary artery disease or other cardiopulmonary disease)

B. Clinical Features

1. Fatigue
2. Dyspnea
3. Headache
4. Palpitations
5. Tachycardia
6. Pallor—best noted in the conjunctiva
7. Signs/symptoms of the underlying cause: orthostatic lightheadedness, syncope, or hypotension if acute bleeding; jaundice if hemolytic anemia; blood in stool if GI bleeding

Quick HIT

Pseudoanemia or dilutional anemia refers to a decrease in Hb and Hct secondary to dilution (i.e., secondary to acute volume infusion or overload). This is a diagnosis of exclusion; all cell lines on a complete blood count should drop proportionally in the right clinical context.

C. Diagnosis

1. Decreased Hb and Hct
   a. Formula for converting Hb to Hct: Hb × 3 = Hct (1 unit of packed RBCs [PRBCs] increases Hb level by 1 point and Hct by 3 points).
   b. Hb of 7 to 8 provides sufficient oxygen-carrying capacity for most patients—anemia is *not* tolerated as well in patients with impaired

cardiac function (see Clinical Pearl 9-1).

2. Reticulocyte index
   a. Reports the number of reticulocytes present as a percentage of the total number of RBCs.
   b. A corrected reticulocyte index to account for degree of anemia can be calculated (in states of anemia, reticulocyte production should increase accordingly).
   c. The reticulocyte count is an important initial test in evaluating anemia because it indicates whether effective erythropoiesis is occurring in the bone marrow.
   d. Effective erythropoiesis is dependent on adequate raw materials (iron, vitamin B_{12}, folate) in the bone marrow, absence of intrinsic bone marrow disease (e.g., aplastic anemia), adequate erythropoietin from the kidney, and survival of reticulocytes (no premature destruction before leaving the bone marrow)—see Clinical Pearl 9-2.
   e. A reticulocyte index >2% implies the bone marrow is responding to increased RBC requirements
   f. A reticulocyte index <2% implies inadequate RBC production by the bone marrow

CLINICAL PEARL 9-1

Transfusion Pearls

- PRBCs (contain no platelets or clotting factors)
  - Mix with normal saline to infuse faster (not with lactated Ringer solution because calcium causes coagulation within the IV line)
  - Each unit raises the hematocrit by 3 to 4 points
  - Each unit may be given to an adult for over 90 to 120 minutes
  - Always check CBC after the transfusion is completed
- FFP
  - Contains all of the clotting factors
  - Contains no RBCs/WBCs/platelets
  - Given for high PT/PTT, coagulopathy, and deficiency of clotting factors—FFP can be given if you cannot wait for vitamin K to take effect, or if patient has liver failure (in which case vitamin K will not work)
  - Follow up PT and PTT to assess response
- Cryoprecipitate
  - Contains factor VIII and fibrinogen
  - For hemophilia A, decreased fibrinogen (DIC) and vWD
- Platelet transfusions—1 unit raises platelet count by 10,000
- Whole blood only for massive blood loss
- For any patient with massive blood loss, the ideal ratio of platelets: FFP: PRBCs which are transfused should be 1:1:1. In addition, during massive blood transfusions, blood should be warmed to prevent a decrease in core body temperature.

Quick HIT

If Hb and Hct reveal anemia, the next tests to obtain to determine cause of anemia are reticulocyte count and MCV.

Quick HIT

Note that all causes of anemia are initially normocytic because it takes some time for the abnormal-sized RBCs to outnumber the normal-sized ones.

CLINICAL PEARL 9-2

Hemolytic Transfusion Reactions Are Divided Into Intravascular and Extravascular Hemolysis

- **Intravascular hemolysis** (also called acute hemolytic reactions):
  - Very serious and life-threatening—caused by ABO-mismatched blood transfused into patient (usually due to clerical error). For example, if B blood is given to a type A patient, anti–B IgM antibodies attach to all of the infused B RBCs, activate the complement pathway, and produce massive intravascular hemolysis as C9 punches holes through RBC membranes.
  - Symptoms include fever/chills, nausea/vomiting, pain in the flanks/back, chest pain, and dyspnea
  - Complications include hypovolemic shock (hypotension, tachycardia), DIC, and renal failure with hemoglobinuria
  - Management involves stopping the transfusion immediately and aggressively replacing the fluid to avoid shock and renal failure, epinephrine for anaphylaxis, dopamine/norepinephrine as needed to maintain blood pressure
- **Extravascular hemolysis** (also called delayed hemolytic transfusion reaction):
  - Extravascular hemolysis is less severe and in most cases is self-limited; it may occur within 3 to 4 weeks after a transfusion
  - It is caused by one of the minor RBC antigens. For example, if a patient is Kell antigen-negative and has anti–Kell IgG antibodies from a previous exposure to the antigen, reexposure of her memory B cells to Kell antigen on RBCs will result in synthesis of IgG anti-Kell antibodies. These antibodies coat all of the Kell antigen-positive donor RBCs, which will be removed extravascularly by macrophages in the spleen, liver, and bone marrow.
  - Symptoms are subtle and include fever, jaundice, and anemia
  - No treatment required—the prognosis is good

3. RBC indices
   a. Mean corpuscular volume (MCV) is the average size of a patient’s RBCs
   b. Mean corpuscular hemoglobin (MCH) is the average Hb content of a patient’s RBCs
   c. Mean corpuscular hemoglobin concentration (MCHC) is the average Hb concentration in each RBC
   d. RDW is the variation in RBC size
4. Peripheral blood smear

D. Diagnosing the Cause of Anemia (General Approach)

1. If the reticulocyte index is <2%, indicating an inadequate bone marrow response, examine the peripheral blood smear and RBC indices (Figure 9-1)
   a. If microcytic anemia (MCV <80), the differential diagnosis includes the following:
      - Iron-deficiency anemia—most common cause
      - Anemia of chronic disease—iron is present in the body but is not available for Hb synthesis due to iron-trapping in macrophages
      - Thalassemia—defective synthesis of globin chains
      - Sideroblastic anemia (includes lead poisoning, pyridoxine deficiency, toxic effects of alcohol)—defective synthesis of protoporphyrins leading to iron accumulation in mitochondria
   b. If macrocytic anemia (MCV >100), the differential diagnosis includes the following:
      - Megaloblastic anemia due to vitamin B_{12}, folate, or copper deficiency (MCV increases significantly)—defective DNA synthesis leading to nuclear defects in RBCs
      - Liver disease (MCV increases up to 115)—abnormal incorporation of plasma lipoproteins into RBC membranes alters RBC shape and increases their volume
      - Reticulocytosis (MCV increases up to 110)—due to hemolysis, bleeding, etc. Reticulocytes are larger than mature RBCs, resulting in an increase in polychromatophilic RBCs. Associated with an increased RDW (multiple RBC populations of differing size and age)
      - Alcohol use disorder
      - Hypothyroidism
   c. If normocytic anemia (MCV 80 to 100), the differential diagnosis includes the following:
      - Aplastic anemia—bone marrow failure
      - Bone marrow fibrosis
      - Bone marrow infiltration
      - Anemia of chronic disease
      - Renal failure—decreased erythropoietin production results in decreased erythropoiesis

- Nutrient deficiency (early stages of iron, vitamin B_{12}, folate, or copper deficiency)

2. If the reticulocyte index is >2%, indicating an adequate bone marrow response, the differential diagnosis includes the following:
   a. Acute blood loss
   b. Hemolysis

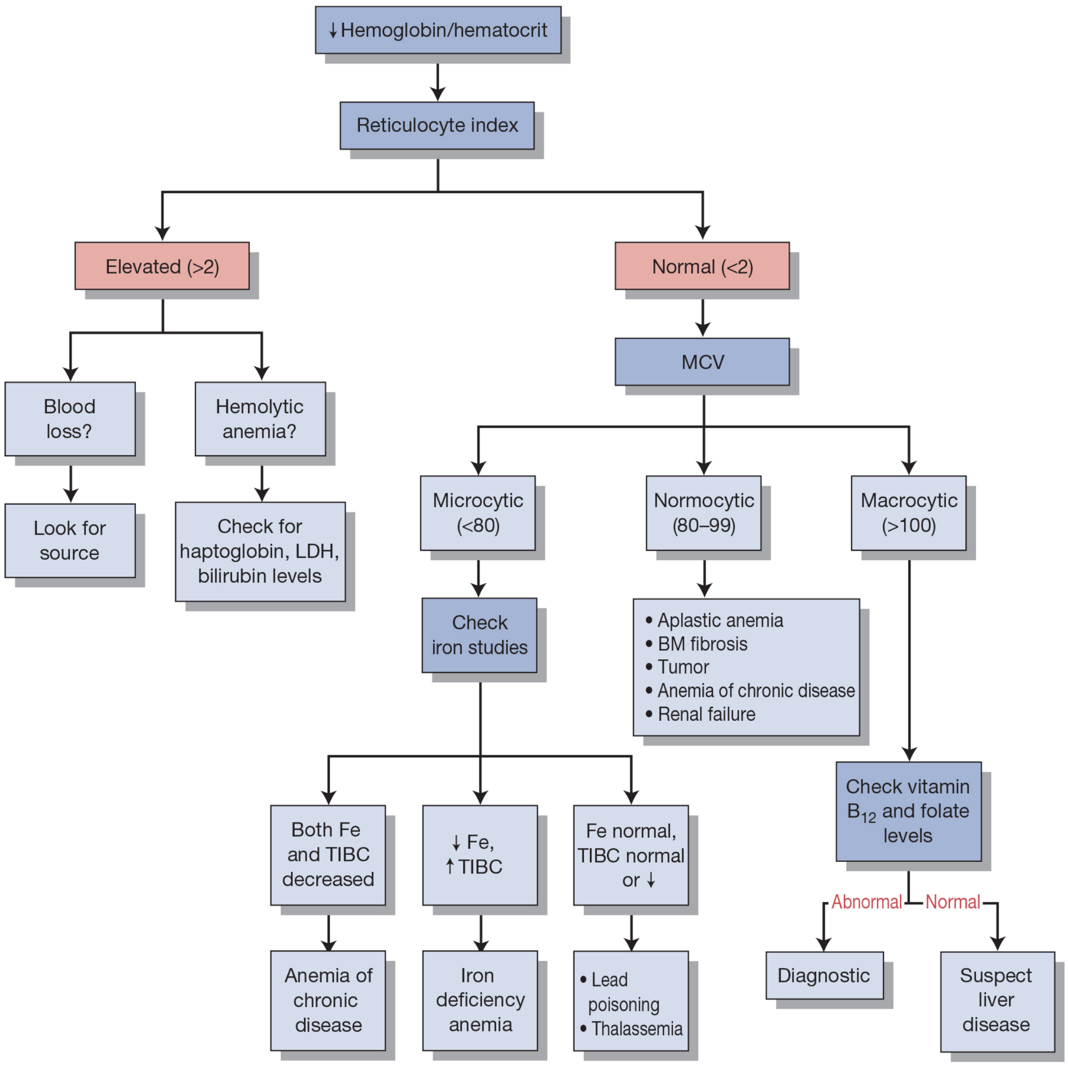


FIGURE 9-1 **Evaluation of anemia.**

Quick HIT

The first step in evaluation of the anemic patient is to assess volume status and hemodynamic stability, in order to identify any active bleeding. If hemodynamically unstable, transfuse PRBCs before attempting to find the source.

Microcytic Anemias

Iron-Deficiency Anemia

A. Causes

1. Chronic blood loss
2. Most common cause of iron-deficiency anemia in adults
3. Menstrual blood loss is the most common source—in the absence of menstrual bleeding, GI blood loss is most likely
4. Dietary deficiency/increased iron requirements, which are primarily seen in the following three age groups:
   a. Infants and toddlers—occurs especially if the diet is predominantly human milk, which is low in iron; children in this age group also have an increased requirement for iron due to accelerated growth
   b. Adolescents—increased requirement for iron due to rapid growth; adolescents who menstruate are particularly at risk due to loss of menstrual blood
   c. Pregnant individuals—pregnancy increases iron requirements

Quick HIT

In elderly patients with iron-deficiency anemia, you must rule out colon cancer.

Quick HIT

Pica (the craving for nonfood items) and pagophagia (the craving for ice) have been associated with iron-deficiency anemia.

B. Diagnosis

1. Iron studies (see Table 9-1)
   a. Decreased serum ferritin
   b. Increased TIBC/transferrin levels
   c. Decreased transferrin saturation
   d. Decreased serum iron
2. Peripheral blood smear—reveals microcytic, hypochromic RBCs (Figure 9-2)
3. Bone marrow biopsy—reveals absence of stainable iron; this test is technically the gold standard, but typically only indicated if laboratory evidence of iron-deficiency anemia is present and no source of blood loss is found
4. Test the stool for occult blood. Often may need to proceed directly to endoscopy/colonoscopy if pre-test probability for GI bleeding is high—colon cancer is a common cause of GI bleeding in those age 50 years or older

TABLE 9-1 Iron Studies in Microcytic Anemias

	Serum Ferritin	Serum Iron	TIBC	RDW
Iron-Deficiency Anemia	Low	Low	High	High
Anemia of Chronic Disease	Normal/high	Low	Normal/low	Normal
Thalassemia	Normal/high	Normal/high	Normal	Normal/high

C. Treatment

1. Oral iron replacement (ferrous sulfate)
   a. A trial of iron replacement therapy may be given to young, otherwise healthy, menstruating individuals without investigating for additional

sources of blood loss (in nonmenstruating and postmenopausal individuals, attempt to determine the source of blood loss first)
   b. Side effects include constipation, nausea, and dyspepsia
2. Parenteral iron replacement
   a. There are multiple formulations of IV iron (ferric gluconate, ferumoxytol, iron sucrose, iron dextran, others). All are equally effective and have similar adverse effect profile (extremely rare infusion reaction or anaphylaxis)
   b. Preferred over oral iron for the following situations:
      - Poor adherence, poor gut absorption, or GI side effects from oral iron
      - Severe iron deficiency or ongoing blood loss
      - Inflammatory state that interferes with absorption of oral iron
      - Preference to rapidly replete iron instead of over several months
3. Blood transfusion is not recommended unless Hb meets the transfusion threshold (usually <7 g/dL, sometimes higher) or the patient has cardiopulmonary disease

Quick HIT

The MCH and MCHC are neither sensitive nor specific for any diagnosis. However, MCV is very valuable in diagnosing the cause of anemia.

Quick HIT

The RDW measures the variation in RBC size. The RDW is usually elevated in anemias caused by nutritional deficiencies. An increased RDW is called anisocytosis.

Thalassemias

A. General Characteristics

1. Genetically inherited disorders characterized by reduced production of either the α- or β-globin chain of Hb

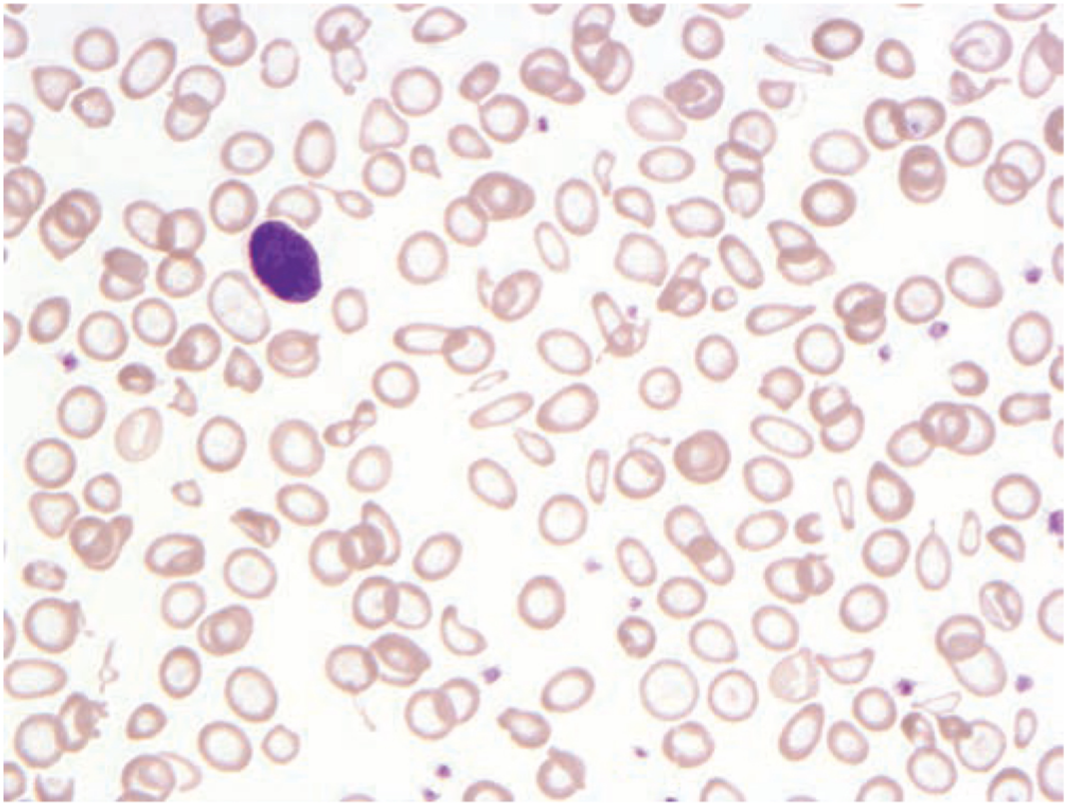


FIGURE 9-2 **Blood smear: iron-deficiency anemia.**
(Reprinted with permission from Pereira I, George TI, Arber DA. *Atlas of Peripheral Blood: The Primary Diagnostic Tool*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.)

2. β-Thalassemias
   a. β-Chain production is decreased, but the synthesis of α-chains is unaffected
   b. Excess α-chains bind to and damage the RBC membrane
   c. Severity depends on the number of alleles mutated and the severity of these mutations
   d. More prevalent among those of Mediterranean, Middle Eastern, and Indian descent
3. α-Thalassemias
   a. There is a decrease in α-chains, which are a component of all types of Hbs
   b. Excess β-globin chains form tetramers, which are abnormal Hbs
   c. Severity depends on the number of alleles that are deleted/mutated, ranging from an asymptomatic carrier state to fetal death

d. More prevalent among those of Southeast Asian and African descent

Quick HIT

Iron overload can develop in patients with transfusion-dependent thalassemia. If untreated, this can lead to CHF and other symptoms of hemochromatosis. These individuals are often treated with iron-chelating agents such as deferoxamine or deferasirox.

B. β-Thalassemias

1. Transfusion-dependent β-Thalassemia (homozygous β-chain thalassemia, previously known as β-thalassemia major)
   a. Clinical features
      - Severe anemia beginning in late infancy
      - Jaundice and dark urine
      - Massive hepatosplenomegaly
      - Expansion of marrow space—can cause distortion of bones and result in "crew-cut" appearance on skull x-ray
      - Growth delay and failure to thrive
      - If untreated, death occurs within the first few years of life secondary to progressive CHF

   b. Diagnosis
      - Hb electrophoresis—reveals elevated Hb F and HbA_2
      - Peripheral blood smear—reveals microcytic, hypochromic anemia; target cells may be seen **(**Figure 9-3**)**

   c. Treatment
      - Frequent PRBC transfusions are required to sustain life
      - Luspatercept (subcutaneous injection that improves RBC maturation) can be used for those with high burden of disease from repeat transfusions
      - Splenectomy may be needed if complications occur
2. Non–transfusion-dependent β-thalassemia (heterozygous β-chain thalassemia, previously known as β-thalassemia minor)
   a. Characterized by asymptomatic carrier state or mild anemia
   b. Diagnosed with Hb electrophoresis
   c. Peripheral blood smear reveals microcytic, hypochromic RBCs

d. Treatment usually not necessary (patients are not transfusion-dependent)

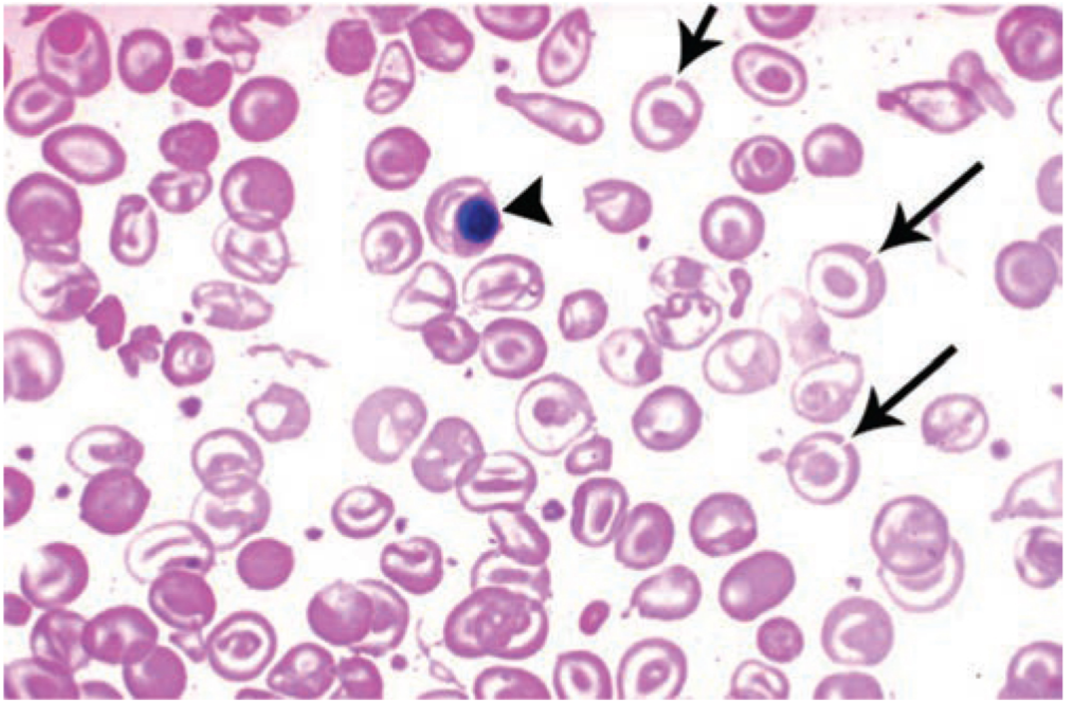


FIGURE 9-3 **Blood smear: thalassemia. Target cells (*arrows*) and circulating nucleated red blood cells (*arrowhead*).**
(Reprinted with permission from Rubin R, Strayer DS, Rubin E. *Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 6th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012:962. Figure 20-15.)

3. β-Thalassemia intermedia
   a. Characterized by anemias of varying severity (when severe, classified under transfusion-dependent β-thalassemia)
   b. Diagnosed with Hb electrophoresis
   c. Peripheral blood smear reveals microcytic, hypochromic RBCs
   d. Most individuals are not transfusion-dependent in childhood, but many will become transfusion-dependent in adulthood

Quick HIT

If iron-deficiency anemia is suspected, but the anemia does not respond to iron therapy, obtain an Hb electrophoresis to rule out α- and β-thalassemia.

C. α-Thalassemias

1. Silent carriers (mutation/deletion of only one α-locus)
   a. Asymptomatic
   b. Normal Hb and Hct level
   c. No treatment necessary
2. α-Thalassemia trait/minor (mutation/deletion of two α-loci)
   a. Characterized by mild anemia
   b. Peripheral blood smear reveals microcytic, hypochromic RBCs
   c. No treatment necessary
3. Hb H disease (mutation/deletion of three α-loci)
   a. Characterized by anemias of varying severity
   b. Hb electrophoresis shows Hb H
   c. Peripheral blood smear reveals microcytic, hypochromic RBCs
   d. Most individuals are not transfusion-dependent, but many require periodic transfusions during episodes of increased hemolysis (e.g., infection)
4. Mutation/deletion of all four α-loci
   a. Either fatal at birth (hydrops fetalis) or shortly after birth

Quick HIT

The most common type of thalassemia is non–transfusion-dependent β-thalassemia (with β-thalassemia minor more common than α-thalassemia minor). Both of these conditions can be mistaken for iron-deficiency anemia.

Sideroblastic Anemia

- Caused by abnormality in RBC iron metabolism leading to pathologic iron deposits in RBC mitochondria.

- May be hereditary or acquired—acquired causes include drugs (e.g., chloramphenicol, INH, linezolid), toxins (lead, alcohol), copper deficiency, collagen vascular disease, and neoplastic disease (e.g., myelodysplastic syndromes).
- Characterized by ringed sideroblasts in bone marrow, increased serum iron, increased serum ferritin, normal TIBC, and normal/elevated TIBC saturation (which distinguishes it from iron-deficiency anemia).
- Treatment involves removing offending agents and transfusing as necessary—may also consider pyridoxine.

Normocytic Anemias

Anemia of Chronic Disease

- Also known as anemia of chronic inflammation
- Occurs in the setting of chronic infection (e.g., tuberculosis, lung abscess), malignancy (e.g., lung, breast, Hodgkin disease), inflammation (e.g., rheumatoid arthritis, systemic lupus erythematosus), or trauma—the release of inflammatory cytokines has a suppressive effect on erythropoiesis and increased hepcidin levels causes low circulating iron levels (iron is retained within reticuloendothelial system)
- Anemia of chronic kidney disease is another subtype of normocytic anemia and is treated with iron supplementation, erythropoiesis-stimulating agents, and PRBC transfusions when needed
- Generally well tolerated
- May be difficult to differentiate from iron-deficiency anemia (both may coexist)
- Laboratory findings include low serum iron, normal-to-low TIBC/serum transferrin, and elevated serum ferritin
- Peripheral blood smear usually reveals normocytic and normochromic anemia, but may be microcytic and hypochromic as well
- No specific treatment is necessary other than treatment of the underlying process—do not give iron unless there is concomitant iron-deficiency anemia

Aplastic Anemia

A. General Characteristics

1. Bone marrow failure leading to pancytopenia (i.e., anemia, neutropenia, thrombocytopenia)
2. Causes
   a. Idiopathic—majority of cases
   b. Radiation exposure
   c. Medications (e.g., antibiotics like sulfonamides, antiseizure agents such as carbamazepine, NSAIDs, antithyroid medications such as methimazole, chloramphenicol)
   d. Viral infection (e.g., human parvovirus, seronegative hepatitis, Epstein–Barr virus [EBV], cytomegalovirus [CMV], herpes zoster, varicella, HIV)
   e. Immune disorders (graft-versus-host disease, SLE)
   f. Chemical exposure (e.g., benzene, solvents, insecticides)

B. Clinical Features

1. Signs/symptoms of anemia: fatigue, dyspnea, headache, palpitations, pallor
2. Signs/symptoms of thrombocytopenia: petechiae, easy bruising, bleeding
3. Increased incidence of infections—due to neutropenia
4. Can transform into acute leukemia

C. Diagnosis

1. Pancytopenia
2. Peripheral blood smear—reveals normocytic anemia with decreased neutrophils and platelets
3. Bone marrow biopsy (for definitive diagnosis)—reveals hypocellular marrow and the absence of progenitors of all three hematopoietic cell lines (Figure 9-4)

D. Treatment

1. Discontinuation of offending agents or treatment of any known underlying causes

2. Transfusion of PRBCs and platelets as necessary—use judiciously
3. Immunosuppressive therapy for severe disease (eltrombopag for bone marrow stimulation, often used in combination with antithymocyte globulin and cyclosporine)
4. Bone marrow transplantation for refractory disease

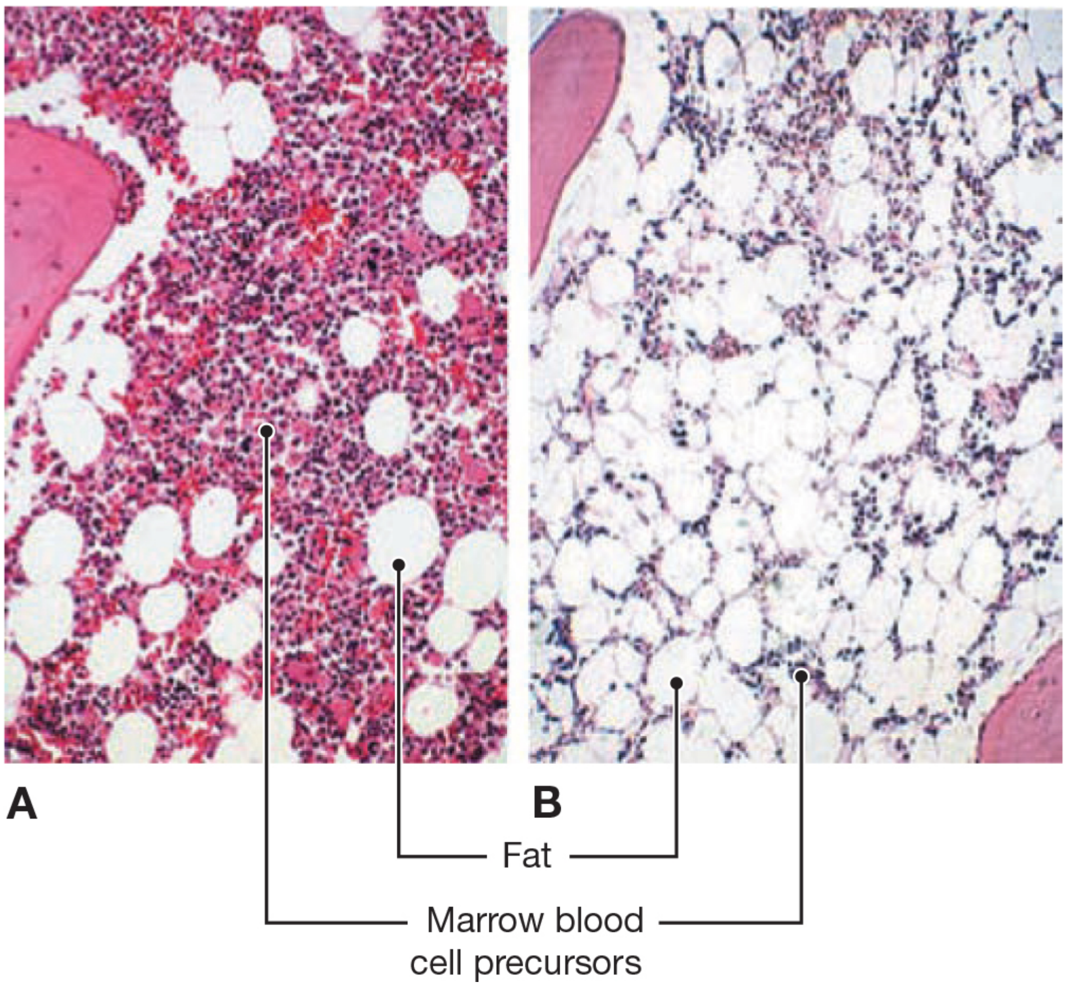


FIGURE 9-4 **Bone marrow biopsy: A. Normal bone marrow. B. Bone marrow in aplastic anemia. Few bone marrow cells are present. Most of the tissue shown is fat.**
(Reprinted with permission from McConnell TH. *The Nature of Disease: Pathology for the Health Professions*. 2nd ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014. Figure 7.9.)

Quick HIT

Pernicious anemia is a special case of vitamin B_{12} deficiency. It is an autoimmune disorder resulting in inadequate production of intrinsic factor, which leads to impaired absorption of vitamin B_{12} in the terminal ileum.

Macrocytic Anemias

Vitamin B_{12} Deficiency

A. General Characteristics

1. Vitamin B_{12} serves as a cofactor in two important reactions required for normal erythropoiesis and CNS functioning:
   a. The conversion of homocysteine to methionine
   b. The conversion of methylmalonyl-CoA to succinyl-CoA
2. The main dietary sources of vitamin B_{12} are foods derived from animal products
3. After ingestion, vitamin B_{12} is bound to intrinsic factor (produced by gastric parietal cells) so it can be absorbed by the terminal ileum
4. Vitamin B_{12} stores in the liver are plentiful and can sustain an individual for 3 or more years
5. Causes
   a. Most commonly due to impaired absorption (either via lack of intrinsic factor or lack of absorptive ileal surface)
   b. Pernicious anemia—lack of intrinsic factor due to autoimmune destruction; most common cause in northern Europe
   c. Gastrectomy—lack of intrinsic factor due to removal of parietal cells
   d. Inadequate dietary intake (e.g., strict veganism, alcohol use disorder)
   e. Crohn disease or resection of terminal ileum (approximately the last 100 cm)
   f. Other organisms competing for vitamin B_{12} (i.e., *Diphyllobothrium latum* infestation [fish tapeworm] and blind loop syndrome [bacterial overgrowth])

Quick HIT

In a patient with megaloblastic anemia, it is important to determine whether folate or vitamin B_{12} deficiency is the cause prior to initiating treatment. Folate supplements can improve the anemia of vitamin B_{12} deficiency, but not the neurologic impairment. Therefore, *if the vitamin B_{12} deficiency remains untreated, irreversible neurologic disease can result.*

Quick HIT

Note that patients with vitamin B_{12} deficiency can have moderate-to-severe neurologic symptoms with little-to-no anemia (i.e., blood counts may be normal). Delay in diagnosis and treatment may lead to irreversible neurologic disease.

B. Clinical Features

1. Sore tongue (stomatitis and glossitis)
2. Neuropsychiatric changes/dementia—look for vitamin B_{12} deficiency in the workup for dementia
3. Neuropathy and subacute combined degeneration of the spinal cord—distinguishes vitamin B_{12} deficiency from folate deficiency
   a. Leads to a loss of position/vibratory sensation in lower extremities, ataxia, and upper motor neuron signs (increased deep tendon reflexes, spasticity, weakness, Babinski sign)
   b. Can lead to urinary and fecal incontinence, impotence

C. Diagnosis

1. Peripheral blood smear—reveals megaloblastic (macrocytic) anemia with hypersegmented neutrophils (Figure 9-5)
2. Low serum vitamin B_{12} level
3. Elevated serum methylmalonic acid and homocysteine levels—most useful if the vitamin B_{12} level is borderline. Homocysteine will be elevated in both folate and B_{12} deficiency; elevated methylmalonic acid is unique to B_{12} deficiency
4. Antibodies to intrinsic factor (for the diagnosis of pernicious anemia)

5. Schilling test was historically used to determine if B_{12} deficiency is due to pernicious anemia, but is not routinely performed. It involved administering IM vitamin B_{12} to saturate binding sites, followed by radiolabeled oral vitamin B_{12}. The amount of radiolabeled B_{12} in the urine and plasma was measured to examine gut absorption. This is then repeated with administration of intrinsic factor, which improves absorption in pernicious anemia

D. Treatment

1. Cyanocobalamin (vitamin B_{12}) IM—parenteral therapy is preferred for symptomatic cases or when impaired gut absorption is suspected.
2. Oral vitamin B_{12} replacement for mild cases. High-dose oral replacement can also be effective for those with impaired gut absorption if dose is sufficiently high.

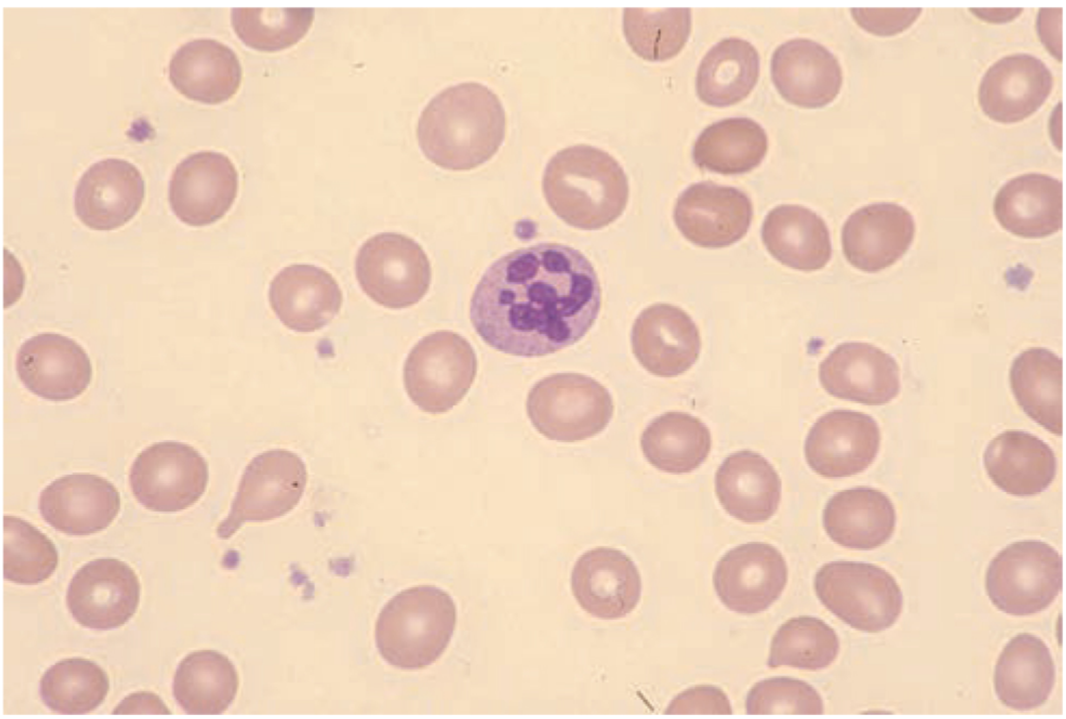


FIGURE 9-5 Blood smear: hypersegmented neutrophil (vitamin B_{12} deficiency).
(Reprinted with permission from Anderson SC, Poulsen KB. *Anderson's Atlas of Hematology*. Lippincott Williams & Wilkins; 2003.)

A 37-year-old man with a history of Crohn disease presents with several months of worsening fatigue. The patient reports 1 to 2 glasses of wine per night with dinner, and does not smoke or use other substances. The patient has also been noting a “pins and needles” sensation in their feet. Physical examination shows conjunctival pallor. Laboratory results reveal the following.

Leukocyte count	5,100/mm^3
Hemoglobin	8.2 g/dL
MCV	110 fL
Platelets	190,000/mm^3

Which of the following is the underlying cause of the patient’s CURRENT symptoms?

A. Anemia of chronic disease
B. Iron deficiency
C. Glucose intolerance
D. Vitamin B_{12} deficiency

- **The answer is D: Vitamin B_{12} deficiency.** The patient in this question likely has cobalamin (vitamin B_{12}) deficiency. This results in a macrocytic anemia. Long-term consequences of vitamin B_{12} deficiency include peripheral neuropathy and posterior column defects from abnormal myelin synthesis. Vitamin B_{12} deficiency results from inadequate vitamin B_{12} intake (diet lacking in animal products) and autoimmune gastritis. The loss of gastric parietal cells secondary to autoimmune gastritis causes intrinsic factor deficiency (which is necessary for vitamin B_{12} absorption in the terminal ileum). **(A)** Anemia of chronic disease is typically microcytic or normocytic. **(B)** Iron deficiency is microcytic anemia (MCV <80 fL) and is not associated with peripheral neuropathy. **(C)** Although glucose

intolerance commonly causes peripheral neuropathy, this patient does not have a history that suggests diabetes.

Quick HIT

The serum homocysteine level is increased in both folate deficiency and vitamin B_{12} deficiency. However, serum methylmalonic acid levels are only seen in vitamin B_{12} deficiency.

Folate Deficiency

A. General Characteristics

1. Folate plays an important role in DNA synthesis
2. Green vegetables and folic acid–supplemented foods are the main dietary sources of folate
3. Folic acid stores in the body are limited, and inadequate intake over a 3-month period can lead to deficiency
4. Causes
   a. Inadequate dietary intake (e.g., “tea and toast” diet, alcohol use disorder, severe anorexia)—most common cause
   b. Increased folate requirements (e.g., pregnancy, chronic hemolysis, hemodialysis)
   c. Use of medications that are folate antagonists (e.g., methotrexate, trimethoprim, valproate, carbamazepine)
   d. Malabsorption syndromes (e.g., celiac disease, gastric bypass surgery)

B. Clinical Features

1. Similar to those of vitamin B_{12} deficiency, but no neurologic symptoms
2. Signs/symptoms of anemia: fatigue, dyspnea, headache, palpitations, pallor
3. Neuropsychiatric changes/dementia—look for folate deficiency in the workup for dementia

C. Diagnosis

1. Peripheral blood smear—reveals megaloblastic (macrocytic) anemia with hypersegmented neutrophils
2. Low serum folate level. Note that serum folate levels can be affected by recent consumption of a meal or folate supplement
3. Elevated serum homocysteine level—methylmalonic acid levels are normal

D. Treatment

1. Daily oral folic acid replacement

Hemolytic Anemias

Overview

A. General Characteristics

1. Hemolysis refers to the premature destruction of RBCs due to a variety of causes.
2. Bone marrow is typically normal and responds appropriately by increasing erythropoiesis, leading to an elevated reticulocyte count. However, if erythropoiesis cannot keep up with the destruction of RBCs, anemia results
3. Hemolytic anemia can be classified according to cause, site, chronicity, or mechanism of destruction
4. Hemolytic anemias are classified based on cause as follows:
   a. Hemolysis due to abnormality extrinsic to RBC—most cases are acquired:
      - Immune-mediated hemolysis
      - Mechanical hemolysis (e.g., prosthetic heart valves, microangiopathic hemolytic anemia)
      - Drug-induced hemolysis (cephalosporins, penicillins, oxaliplatin, etc.)
      - Burns, toxins (e.g., snake bite, brown recluse spider bite), infections (e.g., malaria, clostridium)

b. Hemolysis due to intrinsic RBC defects—most cases are inherited:
   - Hemoglobinopathies (e.g., sickle cell anemia, Hb C disease, thalassemias)
   - Membrane defects (e.g., hereditary spherocytosis [HS], paroxysmal nocturnal hemoglobinuria [PNH])
   - Enzyme defects (e.g., glucose-6-phosphate dehydrogenase [G6PD] deficiency, pyruvate kinase deficiency)

5. Hemolytic anemias are classified based on the predominant site of hemolysis as follows:
   a. Intravascular hemolysis—within the circulation
   b. Extravascular hemolysis—within the reticuloendothelial system, primarily the spleen

Quick HIT

Geographic region of origin, family history of jaundice/anemia, and medications are all relevant aspects of the history of a patient with hemolytic anemia.

Quick HIT

Mechanical heart valves and other intravascular devices can hemolyze RBCs by shear stress and lead to hemolytic anemia.

Quick HIT

Expected Laboratory Results in Hemolytic Anemia

- Elevated reticulocyte count, LDH, indirect bilirubin
- Decreased haptoglobin and Hb/Hct

A 61-year-old woman with a history of diabetes mellitus, hypertension, and mechanical aortic valve replacement presents with fatigue and periodic palpitations when running. The patient does not have shortness of breath or chest pain. Her medications consist of warfarin, metformin, glyburide, lisinopril, and fish oil. On physical examination, she has conjunctival pallor, mechanical click during S2, and a soft systolic flow murmur. A digital rectal examination shows normal stool. Laboratory results reveal a hemoglobin of 10.1 g/dL, hematocrit of 29%, and a significantly elevated serum LDH. The peripheral blood smear shows schistocytes.

Which of the following is the underlying cause of this patient’s condition?

A. Autoimmune hemolysis
B. Iron deficiency
C. Traumatic hemolysis
D. Bone marrow infiltration

- **The answer is C: Traumatic hemolysis.** The patient in this question is presenting with anemia, elevated LDH, and schistocytes on peripheral blood smear. Increased LDH and schistocytes suggest increased red blood cell (RBC) *destruction* (i.e., hemolysis) as opposed to decreased RBC *production.* Traumatic hemolytic anemia is intravascular hemolysis caused by excessive shear or turbulence. As this patient has a mechanical aortic valve, her anemia is most consistent with hemolysis secondary to RBC shearing on the valve. Other findings in the setting of hemolytic anemia include decreased haptoglobin and elevated indirect bilirubin. **(A)** Although autoimmune hemolytic anemia would also demonstrate elevated serum LDH, there will be *spherocytes*, rather than *schistocytes*, on peripheral blood smear. Furthermore, direct antiglobulin test (Coombs test) will be positive. **(B, D)** Iron deficiency and bone

marrow infiltration cause decreased RBC *production* rather than *destruction*.

Quick HIT

Physical injury to RBCs leads to the presence of fragmented RBCs called schistocytes or helmet cells on the blood smear. This can occur in TTP, DIC, and patients with prosthetic heart valves.

B. Clinical Features

1. Signs/symptoms of anemia: fatigue, dyspnea, headache, palpitations, pallor
2. Jaundice
3. Dark urine color if intravascular process—due to hemoglobinuria, not bilirubin
4. Hepatosplenomegaly, cholelithiasis, and lymphadenopathy if chronic
5. Signs/symptoms of underlying disease (e.g., bone crises in sickle cell disease)

C. Diagnosis

1. Low Hb/Hct—level depends on degree of hemolysis and reticulocytosis
2. Elevated reticulocyte count—due to increased RBC production
3. Peripheral blood smear
   a. Schistocytes suggest intravascular hemolysis (“trauma” or mechanical hemolysis) (Figure 9-6)
   b. Spherocytes or helmet cells suggest extravascular hemolysis (depending on the cause)
   c. Sickled RBCs if sickle cell anemia
   d. Heinz bodies if G6PD deficiency
4. Low haptoglobin (especially with intravascular hemolysis)—haptoglobin binds to free Hb, so decreased levels suggest Hb release secondary to RBC destruction

FIGURE 9-6 Blood smear: schistocytes.
(Reprinted with permission from Anderson SC, Poulsen KB. *Anderson's Atlas of Hematology*. Lippincott Williams & Wilkins; 2003.)

5. Elevated LDH—released when RBCs are destroyed
6. Elevated indirect (unconjugated) bilirubin—due to degradation of heme as RBCs are destroyed
7. Positive direct antiglobulin test (DAT) or Coombs test if autoimmune hemolytic anemia (AIHA)—detects antibody or complement on RBC membrane
8. Positive osmotic fragility test (see below)

D. Treatment

1. Treat underlying cause
2. Transfusion of PRBCs if severe anemia is present or patient is hemodynamically compromised
3. Folate supplementation—folate is depleted in hemolysis
4. Plasma exchange may be necessary for cases of thrombotic microangiopathy (TTP, HUS)

Sickle Cell Disease

A. General Characteristics

1. Sickle cell anemia
   a. Autosomal recessive disorder resulting from the inheritance of two Hb S genes (homozygous), causing normal Hb A to be replaced by the mutant Hb S
   b. Hb S is distinguished from Hb A by its substitution of an uncharged valine for a negatively charged glutamic acid at the sixth position of the β-chain
   c. Under reduced oxygen conditions (e.g., acidosis, hypoxia, changes in temperature, dehydration, and infection) the Hb S molecules polymerize, causing the RBCs to sickle. Sickled RBCs obstruct small vessels, leading to ischemia (see Clinical Pearl 9-3)
2. Sickle cell trait
   a. Results from the inheritance of one Hb S gene (heterozygous)
   b. Sickle trait is found in high prevalence in various regions around the world, but highest in Africa. It is also prevalent in South Asia, Europe, the Middle East, and the Caribbean. High prevalence in these regions is thought to be related to the protective effect of sickle trait against severe malarial infection
   c. Patients with sickle cell trait are not anemic and have a normal life expectancy
   d. Sickle cell trait is associated with isosthenuria, the inability to concentrate or dilute urine—patients will have a constant osmolality on urinalysis testing
   e. Screening can identify asymptomatic individuals with sickle cell trait, for whom genetic counseling may be provided
3. Prognosis
   a. In general, sickle cell disease reduces life expectancy, with a median survival of 58 years in the United States
   b. Factors that have been associated with increased mortality rates include greater frequency of hospitalization, acute chest syndrome, renal insufficiency, and low socioeconomic status
   c. The most common causes of death include acute chest syndrome and multiorgan failure

CLINICAL PEARL 9-3

Almost Every Organ Can Be Involved in Sickle Cell Disease

- Blood—chronic hemolytic anemia, aplastic crises
- Heart—high-output CHF due to anemia
- CNS—stroke
- GI tract—gallbladder disease (stones), splenic infarctions, abdominal crises
- Bones—painful crises, osteomyelitis, avascular necrosis
- Lungs—infections, acute chest syndrome
- Kidneys—hematuria, papillary necrosis, renal failure
- Eyes—proliferative retinopathy, retinal infarcts
- Genitalia—priapism

B. Clinical Features

1. Manifestations of chronic, hemolytic anemia
   a. Pallor and/or jaundice
   b. Gallstone disease (pigmented gallstones)
   c. Delayed growth and maturation
   d. High-output heart failure

Quick HIT

Sickle cell crises vary in severity and frequency among patients. Some have many painful events requiring multiple hospitalizations per year, while others have very few. Each episode is typically followed by a period of remission.

Quick HIT

Vaso-occlusive crises are due to obstruction of microcirculation by sickled RBCs. This leads to ischemia in various organs, producing the characteristic “painful crises.”

2. Manifestations of acute vaso-occlusion
   a. Pain crises—most common clinical manifestation
   b. Vaso-occlusion results in bone infarction, causing severe pain

c. Bone pain usually involves multiple sites (e.g., tibia, humerus, femur) and may or may not be bilateral
d. Pain is self-limiting and usually lasts 2 to 7 days
e. Hand-foot syndrome (dactylitis)
   - Painful swelling of dorsa of hands and feet seen in infancy and early childhood (usually 4 to 6 months)
   - Often the first manifestation of sickle cell disease
   - Caused by avascular necrosis of the metacarpal and metatarsal bones
f. Acute chest syndrome
   - Clinical presentation similar to pneumonia
   - Characterized by chest pain, respiratory distress, pulmonary infiltrates, and hypoxia
   - Due to repeated episodes of pulmonary infarctions
g. Splenic infarction
   - Recurrent episodes eventually lead to autosplenectomy, whereby the spleen is reduced to a small, calcified remnant
   - The spleen is large in childhood but is no longer palpable by 4 years of age
h. Priapism
   - Erection due to vaso-occlusion, usually lasting between 30 minutes and 3 hours
   - Usually subsides spontaneously, after urine is passed, after light exercise, or after a cold shower. Sustained priapism (i.e., lasting more than 3 hours) is rare (less than 2%), but is a medical emergency
i. Renal infarction—common, affecting up to 20% of patients
   - Characterized by hematuria (usually painless)
   - Seldom requires hospitalization and may cease spontaneously
j. Venous thromboembolism
k. Stroke—primarily in children
l. Myocardial infarction
m. Avascular necrosis of joints—most common in hip and shoulder

Quick HIT

Splenic Sequestration Crisis

- Sudden pooling of blood into the spleen results in rapid development of splenomegaly and hypovolemic shock
- A potentially fatal complication of sickle cell disease (and β-thalassemia) occurring more commonly in children (because they have intact spleens)

3. Manifestations of chronic vaso-occlusion
   a. Chronic lower extremity ulcers—most common over lateral malleoli
   b. Pulmonary hypertension
   c. Osteoporosis
   d. Ophthalmologic complications (e.g., retinal infarcts, vitreous hemorrhage, proliferative retinopathy, retinal detachment)
   e. Chronic pain
   f. Chronic psychosocial issues (reduced quality of life, anxiety, depression)
4. Aplastic crises
   a. Usually provoked by a viral infection such as human parvovirus B19, which reduces the ability of the bone marrow to compensate for chronic hemolysis
5. Infectious complications
   a. Functional asplenia results in increased susceptibility to infections (particularly encapsulated bacteria such as *Haemophilus influenzae, Streptococcus pneumoniae*)
   b. Predisposition to *Salmonella* osteomyelitis (encapsulated organism)

C. Diagnosis

1. Anemia—most common finding
2. Peripheral blood smear—reveals sickle-shaped RBCs (Figure 9-7)
3. Hb electrophoresis—required for diagnosis, although most patients are diagnosed on newborn screening

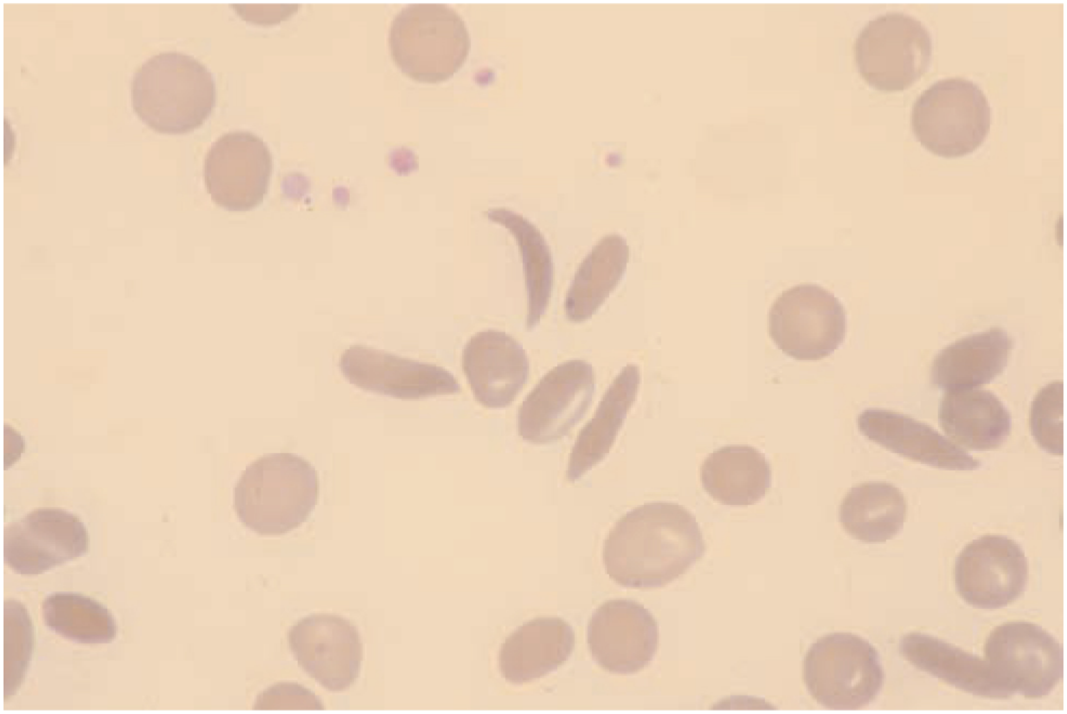


FIGURE 9-7 **Blood smear: sickle cell disease.**
(Reprinted with permission from Anderson SC, Poulsen KB. *Anderson's Atlas of Hematology*. Lippincott Williams & Wilkins; 2003.)

D. Treatment

1. Prevention of crises
   a. Avoid high altitudes—low oxygen tension can precipitate crisis
   b. Maintain fluid intake—dehydration can precipitate crisis
   c. Treat infections promptly—infection/fever can precipitate crisis and should be considered a medical emergency
2. Prevention of infections
   a. Early vaccination for *S. pneumoniae, H. influenzae,* and *Neisseria meningitidis*
   b. Prophylactic penicillin for children <5 years of age
3. Hydroxyurea
   a. Indicated for adults with severe/symptomatic sickle cell disease, frequent pain crises, severe/recurrent acute chest syndrome, or chronic pain
   b. Enhances Hb F levels, which reduce sickling

c. Reduces vaso-occlusive events, including pain crises and acute chest syndrome
4. Management of anemia
a. Folic acid supplementation
b. Blood transfusion as necessary—base need for transfusion on the patient's clinical condition and not on Hb levels (e.g., the presence of vaso-occlusive phenomena such as acute chest syndrome, stroke, or cardiac decompensation)
5. Management of acute painful episodes
a. Hydration—oral hydration if mild episode, IV fluids (normal saline) for moderate/severe episodes
b. Opioids and other analgesic therapy for pain control—do not underestimate patient's pain; the patient's report of pain is the gold standard for assessment
6. Bone marrow transplantation—has been performed successfully to cure sickle cell anemia, but is not routinely performed due to matched donor availability and risk of complications

Quick HIT

Causes of Spherocytosis

- Hereditary spherocytosis
- G6PD deficiency
- ABO incompatibility (but not Rh incompatibility)
- Hyperthermia
- AIHA

Hereditary Spherocytosis

A. General Characteristics

1. HS is caused by the autosomal dominant inheritance of a defect in the gene coding for spectrin and other RBC proteins.
2. There is a loss of RBC membrane surface area without a reduction in RBC volume, necessitating a spherical shape. The spherical RBCs

become trapped and destroyed in the spleen (by macrophages)—hence the term extravascular hemolysis.

B. Clinical Features

1. Hemolytic anemia—can be severe
2. Jaundice
3. Splenomegaly
4. Gallstones
5. Occasional hemolytic crises

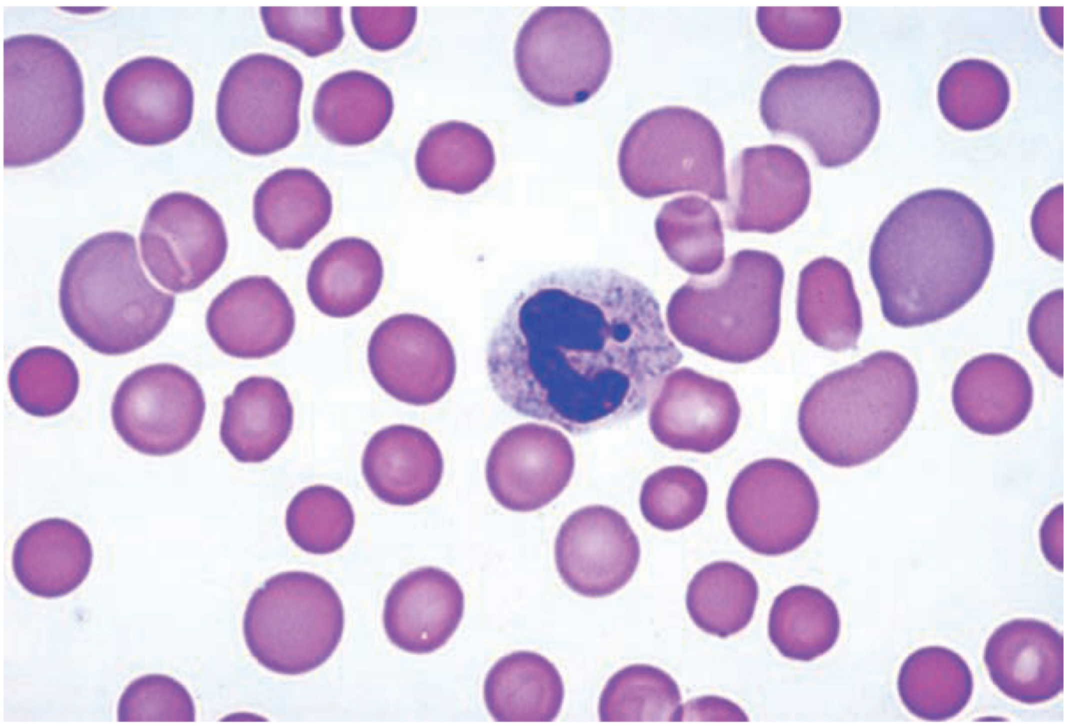


FIGURE 9-8 **Blood smear: spherocytes (hereditary spherocytosis).**
(Reprinted with permission from Strayer DS, Rubin E. *Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 7th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014:1094. Figure 26-17.)

C. Diagnosis

1. Microcytic anemia
2. Elevated reticulocyte count
3. Elevated MCHC

4. Peripheral blood smear—reveals spherocytes (sphere-shaped RBCs) (Figure 9-8)
5. Negative DAT or Coombs test—helps to distinguish HS from AIHA (also characterized by spherocytes)
6. Eosin-5-maleimide (EMA) binding testing
7. EMA is a dye that binds to several proteins present on the RBC membrane
8. Spherocytes have a reduced number of these proteins present on their membranes and will demonstrate decreased EMA binding on testing
9. Osmotic fragility testing
   a. Tests the ability of RBCs to swell in a graded series of hypotonic solutions
   b. Because of their reduced surface area to volume ratio, spherocytes are less tolerant of swelling and will rupture earlier (in more concentrated solutions) than normal RBCs (they are osmotically fragile)

Quick HIT

Following splenectomy, patients must be immunized against encapsulated organisms—*N. meningitidis, S. pneumoniae, H. influenzae.*

D. Treatment

1. Blood transfusion and folate supplementation as necessary
2. Splenectomy in patients with symptomatic or moderate/severe anemia

Glucose-6-Phosphate Dehydrogenase Deficiency

A. General Characteristics

1. X-linked recessive disorder that primarily affects men
2. Most common inherited RBC enzymatic defect
3. Known precipitants include sulfonamides, nitrofurantoin, primaquine, dapsone, rasburicase, fava beans, and infection
4. Specific variants are more common in certain populations:

a. G6PD A$^-$ variant

- A mild form of G6PD deficiency is the most common variant in individuals of African ancestry
- In this form, enzymatic activity is preserved in young RBCs, but declines as RBCs age
- Because hemolysis is limited to the older, enzyme-deficient RBCs, hemolytic episodes are usually mild and self-limited
- Hemolytic episodes are usually triggered by infection or by certain drugs, such as antimalarials (e.g., primaquine) and sulfur-containing antibiotics (e.g., sulfonamide or trimethoprim sulfamethoxazole)

b. G6PD Mediterranean variant

- More severe form of G6PD deficiency, most common in individuals of Mediterranean descent
- In this form, the majority of RBCs are enzyme-deficient (young as well as old RBCs)
- Causes severe hemolytic anemia, especially when exposed to fava beans
- May require transfusions until the inciting agent is eliminated from the body

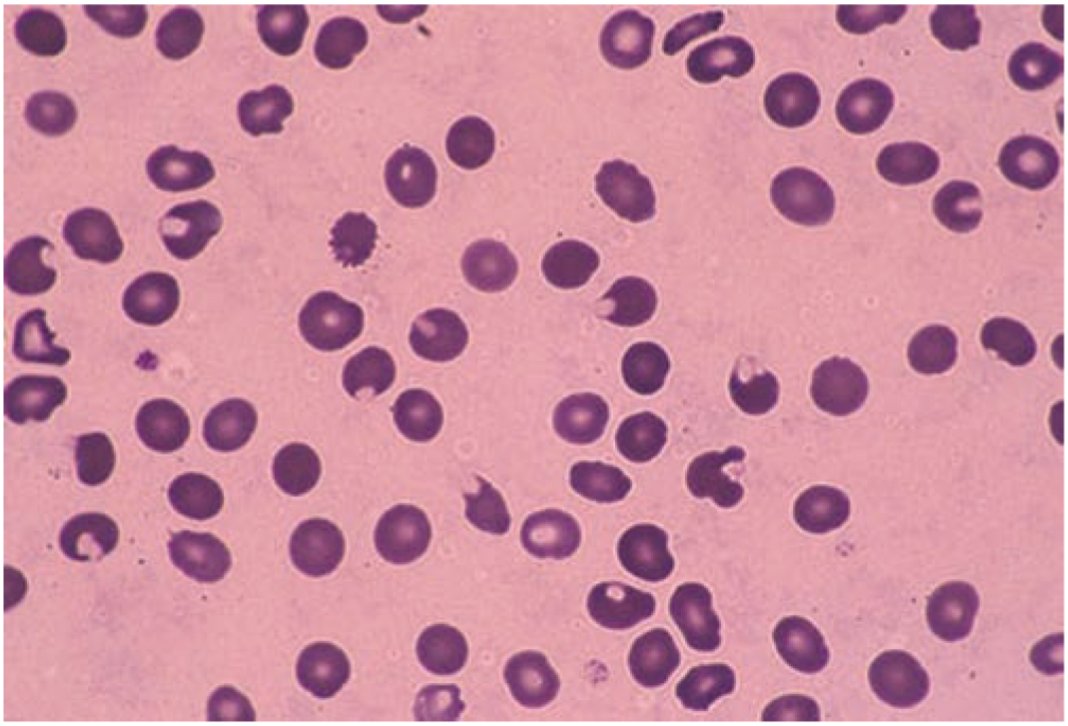


FIGURE 9-9 **Blood smear: bite cells (glucose-6-phosphate dehydrogenase deficiency).**
(Reprinted with permission from Farhi DC, Chai CC, Edelman AS, et al. *Pathology of Bone Marrow and Blood Cells*. Lippincott Williams & Wilkins; 2004.)

Quick HIT

- Deficiency of G6PD results in the accumulation of H_2O_2 in RBCs, which denatures Hb and precipitates Heinz body formation within RBCs.
- Heinz bodies attach to RBC membranes, reducing their flexibility and making them prone to splenic sequestration.

B. Clinical Features

1. Episodic hemolytic anemia—usually induced by drugs, foods, or illness
2. Dark urine
3. Jaundice

C. Diagnosis

1. Anemia, elevated LDH, decreased haptoglobin, and elevated indirect bilirubin (during episodes of hemolysis)
2. Peripheral blood smear
   a. "Bite cells"—RBCs that appear to have "bites" taken out of them, secondary to phagocytosis of Heinz bodies by splenic macrophages (Figure 9-9)
   b. Heinz bodies—abnormal Hb precipitates within RBCs
3. G6PD assay—reveals deficient NADPH formation
4. Decreased G6PD level is diagnostic—important to note that G6PD levels may be normal during acute hemolytic episodes, because RBCs most deficient in G6PD have already been destroyed; repeating the test approximately 3 months after hemolytic episode facilitates diagnosis

D. Treatment

1. Avoid drugs or other exposures that precipitate hemolysis
2. Maintain hydration
3. Blood transfusion as necessary

Autoimmune Hemolytic Anemia

A. General Characteristics

1. Production of autoantibodies to RBC membrane antigen(s) which leads to hemolysis
2. The type of antibody produced (IgG or IgM) determines the prognosis, site of RBC destruction, and response to treatment
3. The course is variable, but tends to be more fulminant in children than in adults
4. Warm AIHA—more common than cold AIHA
   a. Autoantibody is IgG, which binds optimally to RBC membranes at 37°C ("warm" temperatures)
   b. Results in extravascular hemolysis—the primary site of RBC sequestration is the spleen, and splenomegaly is a common feature
   c. May be primary/idiopathic or secondary to lymphomas, leukemias (e.g., chronic lymphocytic leukemia), other malignancies, collagen

vascular diseases (especially SLE), and drugs (e.g., α-methyldopa)

5. Cold AIHA
   a. Autoantibody is IgM, which binds optimally to the RBC membrane at 0° to 5°C ("cold" temperatures)
   b. Results in complement activation and intravascular hemolysis—primary site of RBC sequestration is the liver
   c. May be primary/idiopathic (especially in the elderly) or secondary to infection (e.g., *Mycoplasma pneumoniae* infection, infectious mononucleosis)

B. Clinical Features

1. Signs/symptoms of anemia: fatigue, dyspnea, headache, palpitations, pallor
2. Jaundice if significant hemolysis is present
3. Signs/symptoms of the underlying disease

C. Diagnosis

1. Anemia with elevated reticulocyte count
2. Elevated LDH
3. Decreased haptoglobin
4. Elevated indirect bilirubin
5. Peripheral blood smear—reveals spherocytes if warm AIHA, or RBC aggregates if cold AIHA
6. DAT or Coombs test
   a. If positive for IgG on RBCs, suggests a diagnosis of warm AIHA
   b. If positive for complement alone on RBCs, suggests a diagnosis of cold AIHA
7. Positive cold agglutinin titer if cold AIHA

A 27-year-old woman presents with shortness of breath and worsening fatigue for the last month. She has a history of type 2 diabetes mellitus and mild intermittent asthma. Her family history is significant for breast cancer and hypertension. On physical examination, her blood pressure is 108/72 mmHg, heart rate is 102 beats per minute, and respiratory rate is 14 breaths per minute. There is conjunctival pallor and scleral icterus. Laboratory results reveal the following.

Leukocyte count	9,600/mm^3
Hemoglobin	7.2 g/dL
MCV	84 fL
Platelets	192,000/mm^3
Total bilirubin	5.4 mg/dL
Direct bilirubin	0.9 mg/dL
Indirect bilirubin	4.5 mg/dL
Serum lactate dehydrogenase	368 U/L
Serum haptoglobin	14 mg/dL (normal range 30–200 mg/dL)
Direct antiglobulin (Coombs) test	positive

Peripheral blood smear shows spherocytes without central pallor.

Which of the following is the most likely diagnosis in this patient?

A. Iron-deficiency anemia
B. Hereditary spherocytosis
C. Autoimmune hemolytic anemia (AIHA)

D. Vitamin B_{12} deficiency

- **The answer is C: Autoimmune hemolytic anemia (AIHA).** The patient in this question is presenting with symptoms and signs consistent with a hemolytic anemia. Hemolytic anemias cause elevated total and indirect bilirubin, elevated LDH, and decreased haptoglobin. This patient's peripheral blood smear shows spherocytes without central pallor, which can be seen in both AIHA and hereditary spherocytosis. **(B)** However, AIHA has a positive DAT/Coombs test whereas hereditary spherocytosis has a negative DAT/Coombs test, positive osmotic fragility test, and a strong family history (it is autosomal dominant). **(A)** Iron-deficiency anemia causes microcytic anemia and this patient has normocytic anemia. **(D)** Vitamin B_{12} deficiency causes macrocytic anemia.

D. Treatment

1. The therapeutic approach depends on the type of autoantibody causing the hemolysis
2. Warm AIHA
   a. Glucocorticoids with or without rituximab—mainstay of therapy
   b. Immunosuppression (cyclophosphamide, mycophenolate mofetil, or azathioprine)—for patients whose condition does not respond to glucocorticoids and rixutimab
   c. RBC transfusions as necessary
   d. Folic acid supplementation
   e. Splenectomy—for refractory disease
3. Cold AIHA
   a. Avoiding exposure to cold—prevents bouts of hemolysis
   b. Rituximab
   c. Various chemotherapy agents
   d. RBC transfusions as necessary
   e. Steroids and splenectomy are *not* beneficial

Paroxysmal Nocturnal Hemoglobinuria

A. General Characteristics

1. Acquired disorder that affects hematopoietic stem cells and cells of all blood lineages
2. Caused by a deficiency of proteins that anchor complement-inactivating proteins to blood cell membranes. This deficiency results in an unusual susceptibility to complement-mediated lysis of RBCs, WBCs, and platelets.

B. Clinical Features

1. Signs/symptoms of anemia: fatigue, dyspnea, headache, palpitations, pallor
2. Signs/symptoms of chronic intravascular hemolysis: paroxysmal hemoglobinuria (dark urine), jaundice
3. Pancytopenia
4. Thrombosis—primarily of venous systems (e.g., of the hepatic veins [Budd–Chiari syndrome])
5. May evolve into aplastic anemia, myelodysplasia, myelofibrosis, and acute leukemia
6. Abdominal, back, and musculoskeletal pain

C. Diagnosis

1. Normocytic anemia with elevated reticulocyte count
2. Elevated LDH
3. Reduced haptoglobin
4. Elevated indirect bilirubin
5. Peripheral blood smear—reveals normochromic, normocytic RBCs
6. Flow cytometry of anchored cell surface proteins (CD55, CD59)

D. Treatment

1. C5 complement inhibitors (eculizumab, ravulizumab)—monoclonal antibodies that serve as a complement inhibitors, for patients with significant disease manifestations (e.g., transfusion dependence, renal insufficiency, or thrombosis)
2. Folic acid supplementation

3. Blood transfusion as necessary
4. Bone marrow transplantation—potentially curative

Platelet Disorders

Thrombocytopenia

A. General Characteristics

1. Defined as platelet count <150,000 (normal range is 150,000 to 400,000/mL) (Figure 9-10)
2. Causes (Figure 9-11)
   a. Decreased production
      - Bone marrow failure: acquired (e.g., aplastic anemia), congenital (e.g., Fanconi syndrome), congenital intrauterine rubella
      - Bone marrow invasion: tumors, leukemia, fibrosis
      - Bone marrow injury or suppression: drugs (e.g., ethanol, chemotherapy agents), chemicals (e.g., benzene), radiation, infection (sepsis, viral, bacterial, parasitic)
      - Nutritional deficiency (vitamin B_{12}, folate, copper)

   b. Increased destruction
      - Immune: infection, drug-induced, immune thrombocytopenic purpura (ITP), SLE, heparin-induced thrombocytopenia (HIT) type 2, HIV-associated thrombocytopenia
      - Nonimmune: disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), HIT type 1
      - Pregnancy: in setting of preeclampsia or eclampsia (remember HELLP syndrome)

   c. Redistribution
      - Sequestration from splenomegaly
      - Dilutional—after large-volume resuscitation or massive transfusion

Quick HIT

HIT

- HIT type 1: Heparin directly causes platelet aggregation, leading to a mild drop in platelets; seen <48 hours after initiating heparin; no treatment is needed.
- HIT type 2: Heparin induces antibody-mediated injury to platelets, leading to a significant drop in counts; seen 3 to 12 days after initiating heparin; heparin should be discontinued immediately.

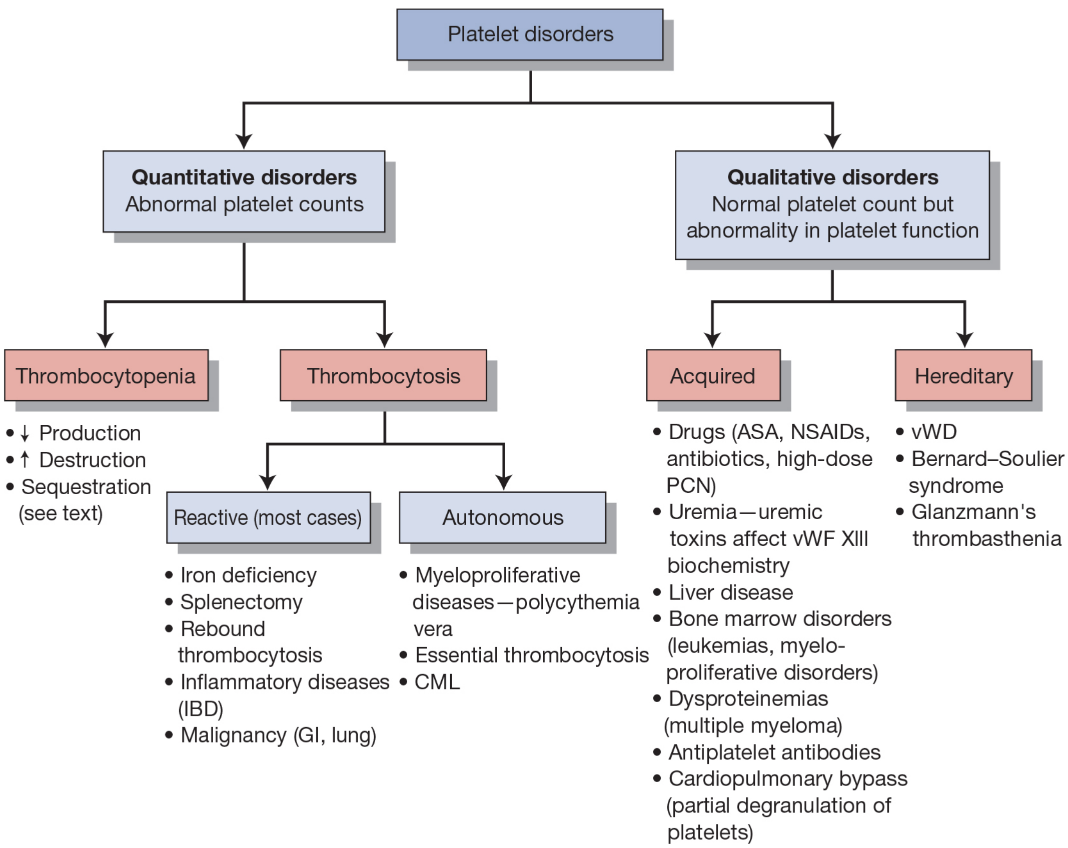


FIGURE 9-10 **Classification of platelet disorders.**

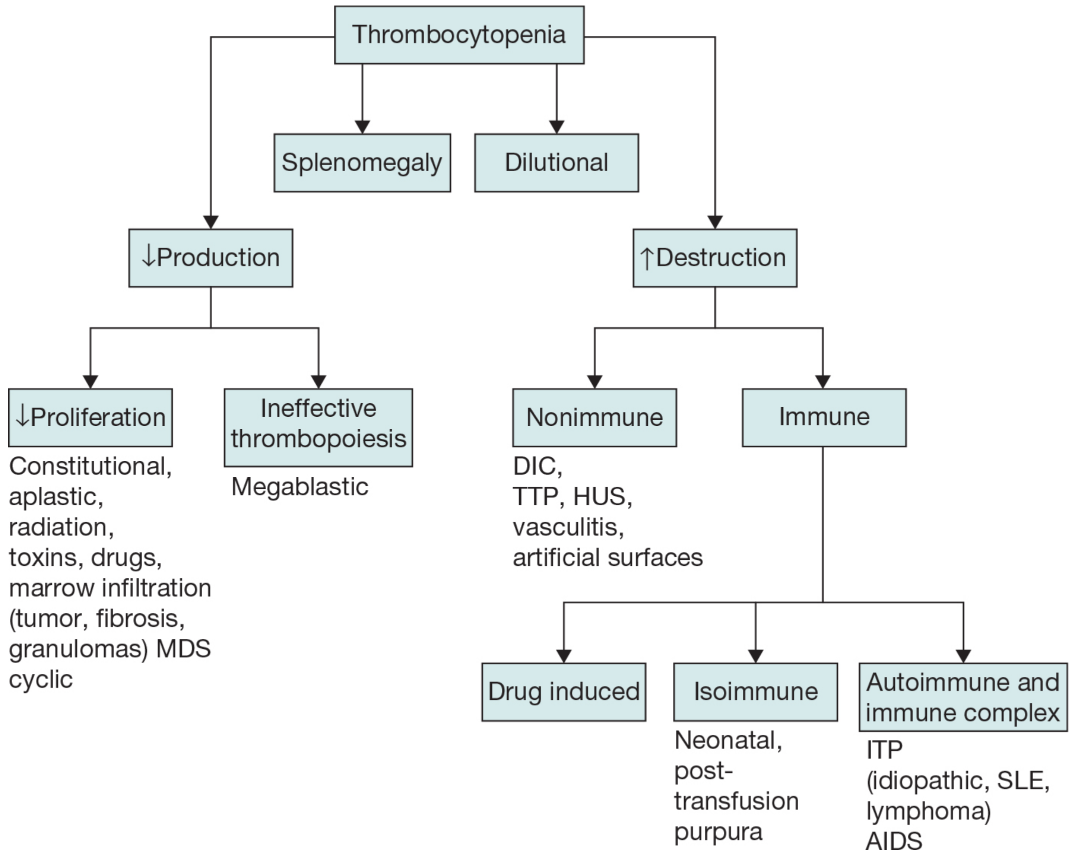


FIGURE 9-11 Etiologies of thrombocytopenia.
(Reprinted with permission from Rao LV, Snyder LM. *Wallach's Interpretation of Diagnostic Tests*. 11th ed. Wolters Kluwer; 2020. Figure 11-3.)

B. Clinical Features

1. Cutaneous bleeding: petechiae (most common in dependent areas), purpura, ecchymoses at sites of minor trauma
2. Mucosal bleeding: epistaxis, menorrhagia, hemoptysis, bleeding in GI and genitourinary (GU) tracts
3. Excessive bleeding after procedures or surgery (when platelet count <50,000)
4. Intracranial hemorrhage and heavy GI bleeding (when platelet count <10,000)—can be life-threatening
5. Do not see heavy bleeding into tissues (hematomas) or joints (hemarthroses) like what is seen in coagulation disorders (e.g., hemophilia)

C. Diagnosis

1. Decreased platelet count
2. Peripheral blood smear
3. Bone marrow biopsy—may be required if primary hematologic disorder is suspected

D. Treatment

1. Remove any offending drugs (e.g., aspirin, NSAIDs, valproate, linezolid) and treat the underlying cause
2. Platelet transfusion as necessary—depending on the cause and severity of thrombocytopenia

Immune (Idiopathic) Thrombocytopenic Purpura

A. General Characteristics

1. IgG autoantibodies to host platelets coat and damage platelets, which are then removed by splenic macrophages (see also Table 9-2)
2. May be acute or chronic:
   a. Acute form
      - Usually seen in children
      - Preceded by a viral infection in most cases
      - Usually self-limited—80% of cases resolve spontaneously within 6 months

   b. Chronic form
      - Usually seen in adults, most commonly in women 20 to 40 years of age
      - Spontaneous remissions are rare

TABLE 9-2 Severity of Thrombocytopenia and Associated Risk

Platelet Count	Risk
>100,000	Abnormal bleeding (even after trauma or surgery) is unusual
20,000–70,000	Increased bleeding hemorrhage during surgery or trauma
<20,000	Minor spontaneous bleeding: easy bruising, petechiae, epistaxis, menorrhagia, bleeding gums
<5,000	Major spontaneous bleeding: intracranial bleeding, heavy GI bleeding

B. Clinical Features

1. Many patients have minimal bleeding symptoms despite extremely low platelet counts (<5,000/mL)
2. Cutaneous bleeding: petechiae, purpura, ecchymoses at sites of minor trauma
3. Mucosal bleeding: epistaxis, menorrhagia, hemoptysis, GI/GU bleeding
4. Splenomegaly is *not* seen

C. Diagnosis

1. Decreased platelet count (frequently less than 20,000)—remainder of the blood count is normal
2. Peripheral blood smear—reveals decreased platelets

D. Treatment

1. First-line therapies
   a. Glucocorticoids—mainstay of therapy
   b. IV immune globulin (IVIG)—saturates the reticuloendothelial system binding sites for platelet-bound self-immunoglobulin, decreasing platelet uptake and destruction by the spleen; typically reserved for patients with active bleeding
2. Second-line therapies

a. Splenectomy—induces remission in 70% to 80% of the cases of chronic, steroid-resistant ITP
b. Rituximab, thrombopoietin receptor agonists (e.g., eltrombopag), and some immunosuppressive agents have been used successfully in splenectomy-resistant patients
3. Platelet transfusions as necessary—generally reserved for critical bleeding or if need to raise platelet count transiently (e.g., for a procedure)

Quick HIT

TTP and HUS

- There is no consumption of clotting factors in TTP, so PT and PTT are normal.
- TTP = HUS + fever + altered mental status
- HUS = microangiopathic hemolytic anemia + thrombocytopenia + renal failure

Quick HIT

Although TTP and HUS may present similarly, renal failure is a more common clinical feature of HUS, while encephalopathy is a common feature of TTP.

Thrombotic Thrombocytopenic Purpura

A. General Characteristics

1. TTP is a rare disorder in which patients lack functional ADAMTS13, a protease that cleaves von Willebrand factor (vWF), resulting in the build-up of ultralarge vWF multimers in the blood
2. This build-up of vWF multimers leads to the formation of microthrombi that consume platelets, occlude small vessels, and cause mechanical damage to RBCs (microangiopathic hemolytic anemia [MAHA])
3. TTP is a life-threatening emergency that can involve any organ. It is highly responsive to therapy (see below), but leads to death if left

untreated.

4. Can be precipitated by systemic disorders (severe hypertension, HELLP syndrome, malignancy), infection (Shiga toxin-mediated HUS), or by drugs (quinine, chemotherapy agents, immunosuppressants)

B. Clinical Features

1. Signs/symptoms of hemolytic anemia: fatigue, dyspnea, pallor, jaundice
2. Signs/symptoms of thrombocytopenia: petechiae, purpura
3. Acute renal failure—typically mild
4. Fever
5. Fluctuating, transient neurologic signs/symptoms—can range from confusion to hemiplegia

C. Diagnosis

1. Anemia
2. Thrombocytopenia
3. Elevated LDH
4. Decreased haptoglobin
5. Elevated indirect bilirubin
6. Peripheral blood smear—reveals schistocytes

D. Treatment

1. Plasmapheresis (therapeutic plasma exchange)—begin as soon as diagnosis is established, can be stopped once platelet count recovers
2. Corticosteroids
3. Rituximab if ADAMTS13 levels are confirmed to be low
4. Anti-VWF therapy (caplacizumab), monoclonal antibody directed against vWF

Heparin-Induced Thrombocytopenia, Type 2

- Two types:

    - Type 1: mild, transient drop in platelet count that is a direct effect of heparin on platelets and not an immune-mediated reaction. This type is not clinically significant as it does not cause thrombosis. Can be managed with observation and does not require discontinuation of heparin products.
    - Type 2: clinically significant syndrome due to antibodies to heparin-platelet factor 4 (PF4) complex
    - Remember the "4 T's": thrombocytopenia (decrease in platelet count typically >50%), timing (onset typically 5 to 10 days after first heparin exposure), thrombosis (secondary to platelet clumping), and lack of other causes for thrombocytopenia.
- Diagnosis is confirmed with antiplatelet factor 4 antibody testing or serotonin release assay.
- Use the 4Ts score to estimate pre-test probability of HIT before sending diagnostic tests. If low probability, generally do not pursue testing due to high rate of false positivity
- Presents with thrombocytopenia, bleeding, and thrombosis
- Treated by discontinuing heparin and initiating anticoagulation (e.g., thrombin inhibitor such as lepirudin, argatroban, and dabigatran)
- Avoid heparin in the future in any patient who has developed an episode of HIT

Quick HIT

Main complication of HIT is venous thrombosis (e.g., DVT or PE).

Bernard–Soulier Syndrome

- Autosomal recessive disease
- Disorder of platelet adhesion (to subendothelium) due to deficiency of platelet glycoprotein GPIb-IX
- On peripheral blood smear, giant platelets and mild thrombocytopenia

Quick HIT

The ristocetin assay can be used to test for vWD.

Glanzmann Thrombasthenia

- Autosomal recessive disease
- Disorder of platelet aggregation due to deficiency in platelet glycoprotein GPIIb–IIIa
- Bleeding time is prolonged
- Platelet count and morphology is normal

Quick HIT

Factor VIII forms a circulating complex with two portions: the coagulant portion (factor VIII coagulant protein) and an antigenic portion (factor VIII antigenic protein). The latter is synonymous with vWF.

Disorders of Coagulation

von Willebrand Disease

A. General Characteristics

1. Most common inherited bleeding disorder, affecting 1% to 3% of the population
2. Autosomal disorder characterized by deficiency or defect of factor VIII–related antigen (vWF). Most types are autosomal dominant, but some have autosomal recessive inheritance (some subtypes of type 2 and type 3 vWD) (see also Table 9-3)
3. vWF enhances platelet aggregation and adhesion (the first steps in clot formation) and acts as a carrier of factor VIII in blood
4. There are three major subtypes with varying severity:
   a. Type 1 (most common)—decreased levels of vWF

b. Type 2 (less common)—dysfunctional vWF protein
c. Type 3 (least common)—absent vWF (very severe disease)

Quick HIT

Other causes of impaired platelet function include uremia and the use of NSAIDs, aspirin, or other antiplatelet agents (e.g., clopidogrel).

B. Clinical Features

1. Cutaneous bleeding: easy bruising
2. Mucosal bleeding: epistaxis, menorrhagia (affects more than 50% of menstruating individuals with von Willebrand Disease [vWD]), bleeding after dental extraction
3. GI bleeding is possible but less common than mucocutaneous bleeding

C. Diagnosis

1. Prolonged bleeding time with normal platelet count
2. PTT may be prolonged if factor VIII level is significantly low—but normal PTT does not exclude the diagnosis
3. Decreased plasma vWF
4. Decreased factor VIII activity
5. Reduced ristocetin-induced platelet aggregation

Quick HIT

- In general, the bleeding seen in vWD is much milder than that of hemophilia—spontaneous hemarthroses do not occur.
- In many patients, diagnosis is not made until prolonged bleeding is noted after surgery or trauma.

D. Treatment

1. DDAVP (desmopressin)—induces release of vWF from endothelial cells
   a. Treatment of choice for type 1 vWD
   b. Less effective in patients with type 2 vWD

c. Ineffective in those with type 3 vWD
d. Used for minor bleeding and minor surgery. Can only be used for 3 to 5 days as tachyphylaxis occurs

2. Factor VIII concentrates (containing high–molecular-weight vWF)
   a. For all patients with vWD (any type) after major trauma, during surgery, or major bleeding (e.g., intracranial or joint bleeding)
   b. Recommended for type 3 vWD (and type 2 patients not responsive to DDAVP)
3. Avoid antiplatelet agents/NSAIDs and intramuscular injections—can exacerbate bleeding tendency

TABLE 9-3 vWF Versus Factor VIII Coagulant Protein

	vWF (also known as Factor VIII–Related Antigenic Protein)	Factor VIII Coagulant Protein
Site of Synthesis	Endothelial cells and megakaryocytes	Liver
Functions	• Platelet adhesion—mediates the adhesion of platelets to the injured vessel walls (i.e., it reacts with platelet GPIb/IX and subendothelium) • Binds the factor VIII coagulant protein and protects it from degradation	Fibrin clot formation
Inheritance Pattern	Most autosomal dominant (some subtypes have recessive inheritance)	X-linked recessive
vWD	Low	Reduced
Hemophilia	Normal	Very low

TABLE 9-4 Classification of Severity of Hemophilia

Classification	Amount (or Activity) of Factor VIII	Clinical Feature
Subclinical	10% of normal factor VIII	Usually asymptomatic
Mild factor VIII deficiency	5–10% of normal factor VIII	Bleeding after injuries/surgery
Moderate factor VIII deficiency	1–5% of normal factor VIII	Rare spontaneous bleeding; severe bleeding after trauma or surgery
Severe factor VIII deficiency—accounts for about 60% of all cases; diagnosed in infancy or early childhood	<1% of normal factor VIII	Spontaneous bleeding in joints (hemarthrosis) and soft tissues; severe hemorrhage after surgery and trauma

Quick HIT

First-line treatment for vWD with mild bleeding is desmopressin. If no response or major bleeding, give factor VIII concentrate.

Hemophilia A

A. General Characteristics

1. X-linked recessive disorder affecting primarily males (approximately 1 in 10,000 male patients)
2. Caused by deficiency or defect of factor VIII coagulant protein
3. Bleeding tendency is related to degree of factor VIII activity (see Table 9-4)

Quick HIT

Suspect hemophilia if unsuspected hemorrhage occurs in a male patient with a positive family history.

B. Clinical Features

1. Hemarthrosis (bleeding into joints)—knee is the most common site, but any joint can be involved; progressive joint destruction can occur secondary to recurrent bleeding
2. Intracranial bleeding—common cause of death; any head trauma is potentially life-threatening and requires urgent evaluation
3. Intramuscular hematomas
4. Retroperitoneal hematomas
5. Hematuria or hemospermia

C. Diagnosis

1. Prolonged PTT (see also Table 9-4)
2. Mixing study: prolonged PTT will normalize with addition of factors
3. Low factor VIII coagulant level with normal levels of vWF

Quick HIT

Detection of Factor VIII Inhibitor

- If normal plasma is mixed with plasma from a hemophilia patient, PTT becomes normal.
- If PTT fails to normalize, this is diagnostic of the presence of a factor VIII inhibitor.

D. Treatment

1. Factor VIII replacement—may be administered episodically (e.g., for acute bleeding episodes, prior to planned surgery/dental work) or continuously (typically in patients with >2 episodes of hemarthrosis or bleeding)
2. DDAVP—may be helpful in patients with mild disease
3. Acute hemarthrosis

a. Factor VIII infusion as soon as possible
b. Analgesia—avoid aspirin and NSAIDs
c. Immobilization of the joint
d. Ice packs
e. Surgical decompression may be needed if severe

Quick HIT

- PT: reflects extrinsic pathway (prolonged by warfarin)
- PTT: reflects intrinsic pathway (prolonged by heparin)
- Thrombin time: measure of fibrinogen concentration
- Bleeding time: reflects platelet function

Hemophilia B

- X-linked recessive disorder
- Much less common than hemophilia A
- Caused by deficiency of factor IX
- Clinical features are identical to those of hemophilia A
- Treatment involves administration of factor IX concentrates—DDAVP does not play a role in treatment

Quick HIT

- Normal PT = 11 to 15 seconds
- Normal PTT = 25 to 40 seconds
- Normal bleeding time = 2 to 7 minutes

Quick HIT

Whenever a coagulopathy is present, include vitamin K deficiency and liver disease in the differential diagnosis (in addition to DIC):

- Liver disease: PT and PTT are elevated, but TT, and fibrinogen are usually normal
- Vitamin K deficiency: PT is prolonged, but PTT, TT, platelet count, and fibrinogen level S are normal

Disseminated Intravascular Coagulation

A. General Characteristics

1. DIC is characterized by abnormal activation of the coagulation cascade and formation of microthrombi throughout the microcirculation, leading to the consumption of platelets, fibrin, and coagulation factors
2. Widespread thrombi cause fibrinolytic mechanisms to be activated, which subsequently leads to hemorrhage (bleeding and thrombosis occur simultaneously)
3. Most common in critically ill patients, but can occur in healthy patients as well
4. Causes
   a. Infection (especially gram-negative sepsis, although any infection can cause DIC)—most common cause
   b. Obstetric complications (e.g., amniotic fluid emboli, retained dead fetus, abruptio placentae, preeclampsia, acute fatty liver of pregnancy)—placenta and uterus have increased tissue factor
   c. Malignancy (especially acute promyelocytic leukemia [APL], pancreas, gastric, ovarian, brain tumors)
   d. Shock/circulatory collapse
   e. Major tissue injury (e.g., trauma, major surgery, burns, fractures, amphetamine overdose, rattlesnake or viper bite)

B. Clinical Features

1. Bleeding—more common in acute cases
   a. Superficial hemorrhage (e.g., ecchymoses, petechiae, purpura)
   b. Bleeding from GI tract, GU tract, gingival, or oral mucosa
   c. Oozing from sites of catheters, procedures or incisions
2. Thrombosis—more common in chronic cases
3. End-organ infarction may occur, especially in the CNS and kidney

C. Diagnosis

1. Prolonged bleeding time, PT, PTT, and TT—due to consumption of coagulation factors and platelets (see Table 9-5)
2. Elevated D-dimer and fibrin split products—due to activation of fibrinolytic system

3. Decreased fibrinogen level—note that fibrinogen is usually low but may be normal in DIC (fibrinogen is an acute phase reactant, so may be elevated at baseline in patients with sepsis, malignancy, etc.)
4. Decreased platelet count
5. Peripheral blood smear—reveals schistocytes and helmet cells due to shearing of RBCs by microthrombi in the microcirculation

TABLE 9-5 Laboratory Findings for Bleeding Disorders

Condition	Platelet Count	Bleeding Time	PT	PTT
Hemophilia	NL[a]	NL	NL	Increased
vWD	NL	Increased	NL	Increased
ITP	Decreased	Increased	NL	NL
TTP	Decreased	Increased	NL	NL
DIC	Decreased	Increased	Increased	Increased
Heparin	NL or decreased	NL	NL	Increased
Warfarin	NL	NL	Increased	NL
Liver disease	NL	NL	Increased	Increased

[a]NL, normal.

Quick HIT

Complications of DIC

- Hemorrhage—intracranial bleeding is a common cause of death
- Thromboembolism—stroke, PE, bowel infarction, acute renal failure, arterial occlusion

D. Treatment

1. Treat the underlying cause (e.g., sepsis, malignancy)
2. Supportive measures if severe hemorrhage is present (only temporizing measures):
   a. Blood transfusion as necessary

b. Platelet transfusion for platelet counts ≤10,000 (or ≤50,000 if actively bleeding or need for urgent surgery)
c. Cryoprecipitate (replaces clotting factors and fibrinogen) or FFP (replaces clotting factors) for significantly prolonged PT/PTT or significantly decreased fibrinogen
d. Anticoagulation to prevent thrombosis is controversial—typically only given in rare cases in which thrombosis dominates the clinical picture
e. Other supportive measures include ventilatory support, hemodynamic support, and IV fluids

Quick HIT

All critically ill patients are at risk for DIC.

Vitamin K Deficiency

A. General Characteristics

1. Several clotting factors (II, VII, IX, and X; proteins C and S) depend on vitamin K for synthesis by the liver, where it serves as a key cofactor in posttranslational modification (γ-carboxylation)
2. Vitamin K is obtained through dietary sources (e.g., leafy green vegetables) and synthesis by intestinal bacterial flora
3. Causes of vitamin K deficiency include:
   a. Broad-spectrum antibiotics—due to suppression of gut flora
   b. Inadequate dietary intake
   c. Total parenteral nutrition (TPN)—unless vitamin K is added
   d. Malabsorption of fat-soluble vitamins (e.g., small bowel disease, inflammatory bowel disease, obstructive jaundice, cystic fibrosis)

Quick HIT

The fat-soluble vitamins include vitamins A, D, E, and K.

Quick HIT

Vitamin K deficiency is most commonly seen in critically ill patients (especially those who are NPO and/or receiving antibiotics).

B. Clinical Features

1. Petechiae
2. Purpura
3. Easy bruising
4. Mucosal bleeding
5. Melena
6. Hematuria

Quick HIT

Factor VII has the shortest half-life (3 to 5 hours) of all clotting factors, so prolonged PT is the first laboratory finding.

C. Diagnosis

1. Prolonged PT—first laboratory finding due to the short half-life of factor VII
2. Prolonged PTT—follows as other coagulation factors diminish

D. Treatment

1. Vitamin K replacement (oral or IM for those with malabsorption)—usually takes several days for PT to return to normal. Use IV vitamin K if need to rapidly reverse coagulopathy (infuse slowly to reduce risk of anaphylaxis)
2. FFP if bleeding is severe and emergency treatment is necessary

Coagulopathy of Liver Disease

A. General Characteristics

1. All clotting factors are produced by the liver (except vWF)

2. Note that advanced liver disease can cause both hypo- and hypercoagulability due to multiple abnormalities in hemostasis
3. The overall prognosis for patients with this type of coagulopathy is very poor, since liver disease must be severe for coagulopathy to develop
4. Causes of coagulopathy in liver failure:
   a. Decreased synthesis of clotting factors
   b. Decreased vitamin K absorption due to cholestasis
   c. Thrombocytopenia caused by splenic sequestration of platelets (the result of splenomegaly due to portal hypertension)

Quick HIT

Prolonged PT is a poor prognostic indicator in cirrhosis because synthesis of clotting factors is not significantly impaired until liver disease is advanced.

B. Clinical Features

1. Bleeding—GI bleeding is most common and is primarily due to varices (secondary to portal hypertension), but is exacerbated by coagulopathy

Quick HIT

Coagulopathy of liver disease may present similarly to DIC with prolonged PT/PTT and low fibrinogen. However, schistocytes will be present on blood smear in DIC.

C. Diagnosis

1. Prolonged PT, PTT, and INR
2. Thrombocytopenia
3. Fibrinogen is often low
4. Thromboelastography (TEG) or thromboelastometry (ROTEM) is increasingly being studied in cirrhosis. Current clinical use is predominantly to guide perioperative transfusions during liver transplantation.

D. Treatment

1. If bleeding: supportive care, PRBC, and platelet transfusion. Consider cryoprecipitate transfusion for low fibrinogen. Avoid FFP transfusion in most cases due to large volume load.
2. Before surgery or procedures: do not routinely transfuse FFP to "correct" the PT or INR before a procedure (studies have shown limited clinical benefit and PT and INR do not accurately reflect degree of coagulopathy in cirrhosis). ROTEM and TEG are being used increasingly to guide perioperative hemostasis.
3. Vitamin K if cholestasis is present
4. DVT prophylaxis if hospitalized—although INR is elevated, patients are often prone to clots (not "auto-anticoagulated")

Quick HIT

Patients with antithrombin (AT) deficiency do not respond to heparin. Heparin requires the presence of antithrombin.

Hypercoagulable States

A. General Characteristics

1. Factor V Leiden (activated protein C resistance)
   a. Inherited cause of hypercoagulability (autosomal dominant)
   b. Caused by mutation in factor V gene
   c. Most common hereditary hypercoagulability disorder among White individuals
   d. Protein C unable to inactivate mutated factor V, leading to unregulated prothrombin activation and increased thrombosis
2. Antithrombin (AT) deficiency
   a. Rare inherited cause of hypercoagulability (autosomal dominant)
   b. AT inhibits thrombin, so its deficiency leads to increased thrombosis

Quick HIT

Patients with antiphospholipid antibody syndrome usually have a prolonged PTT during laboratory testing. This is because the antibody interferes with the test, and is a *false* prolongation.

3. Protein C deficiency
   a. Inherited cause of hypercoagulability (autosomal dominant)
   b. Protein C inhibits factors V and VIII, so its deficiency leads to unregulated fibrin synthesis and thrombosis
4. Protein S deficiency
   a. Inherited cause of hypercoagulability (autosomal dominant)
   b. Protein S is a cofactor of protein C, so its deficiency leads to decreased protein C activity and thrombosis

Quick HIT

In many cases, inherited hypercoagulable diseases cause thrombotic events only when other risk factors (e.g., immobilization, pregnancy, surgery) are also present.

5. Antiphospholipid antibody syndrome (APLS)
   a. Acquired cause of hypercoagulability
   b. Caused by autoantibodies to phospholipid-binding proteins, including lupus anticoagulant, anticardiolipin, and β_2-microglobulin
   c. Can present with arterial or venous thrombosis, recurrent fetal loss, or thrombocytopenia
6. Prothrombin gene mutation
7. Hyperhomocysteinemia

CLINICAL PEARL 9-4

Secondary Hypercoagulable States or Risk Factors

- Malignancy (especially pancreas, GI, lung, and ovaries)
- Antiphospholipid antibody syndrome
- Pregnancy—up to 2 months postpartum
- Immobilization
- Myeloproliferative disorders
- Oral contraceptives
- Postoperative state (especially after orthopedic procedures)
- Trauma
- Nephrotic syndrome
- HIT or DIC
- PNH
- Heart failure

B. Clinical Features

1. Recurrent venous thromboembolisms (e.g., DVT and PE)—hypercoagulable disorders are usually not diagnosed until the patient has had several episodes of DVT or PE (see Clinical Pearl 9-4)
2. Thrombosis in unusual sites (e.g., mesenteric veins, inferior vena cava, renal veins, cerebral veins)
3. First thrombotic event before age 40 years
4. Family history of DVT, PE, or recurrent thrombotic events

C. Diagnosis

1. Functional assays are available for AT, antiphospholipid antibodies, protein C, protein S, factor V Leiden, prothrombin gene mutation, and hyperhomocysteinemia.
2. Note that some assays cannot be interpreted immediately after acute thrombosis or while on certain anticoagulants.

Quick HIT

- Consider secondary hypercoagulable states (see Clinical Pearl 9-4) in a young patient with unprovoked DVT, PE, or thrombotic event, especially if recurrent.
- Testing is indicated for young patients (age <45 years), recurrent thrombosis, clots in unusual locations, or arterial thrombosis (test for APLS).
- Testing is otherwise a personal decision with the patient as results may not change management (often lifelong anticoagulation) but can be helpful for genetic counseling.

D. Treatment

1. Standard treatment for DVT or PE as in patients without primary hypercoagulable states
2. Lifelong anticoagulation for patients with recurrent thromboembolic events or persistent high thrombotic risk

Anticoagulation

Heparin

A. Mechanism of Action

1. Potentiates the action of AT III to primarily inhibit clotting factors IIa and Xa, preventing conversion of fibrinogen to fibrin
2. Prolongs PTT
3. Half-life of standard heparin is 1 hour (half-life is longer for LMWHs—3 to 24 hours, depending on the product)

Quick HIT

Options for DVT Prophylaxis in Hospitalized Patients

- LMWH
- Low-dose unfractionated heparin
- Pneumatic compression boots (when high risk of bleeding)

B. Indications for Use

1. Prophylaxis and treatment of venous thromboembolism (e.g., DVT, PE)
2. Atrial fibrillation in acute setting
3. Acute coronary syndromes (e.g., unstable angina, myocardial infarction)

C. Administration

1. Therapeutic dosing usually given intravenously as an initial bolus followed by continuous IV infusion
2. Prophylactic dosing usually given subcutaneously
3. Monitored using PTT or antifactor Xa levels—therapeutic PTT is usually 60 to 90 seconds, although this varies depending on the clinical situation

D. Adverse Effects

1. Bleeding
2. HIT—skin necrosis may occur as a consequence
3. Osteoporosis—with chronic use (>6 months), lower incidence with LMWHs
4. Transient alopecia
5. Hyperkalemia
6. Rebound hypercoagulability after discontinuation—due to depression of AT III

E. Contraindications

1. History of HIT type 2
2. Active bleeding (e.g., GI bleeding, intracranial bleeding)

3. Severe thrombocytopenia
4. Use with caution in severe HTN or after recent surgery (especially of eyes, spine, brain)

Quick HIT

Administer FFP if severe bleeding occurs (for patients on either warfarin or heparin).

F. Reversing the Effects of Heparin and LMWHs

1. The half-life of standard heparin is short, so its effects will cease within 4 hours of discontinuation—LMWH has a longer half-life
2. Protamine sulfate will reverse the effects of heparin, if necessary

Low–Molecular-Weight Heparin

A. Mechanism of Action

1. LMWHs primarily inhibit factor Xa (equivalent inhibition of factor Xa as standard heparin, but less inhibition of factor IIa [thrombin])
2. Cannot be monitored by PT or PTT because they do not affect either
3. Examples include enoxaparin, dalteparin, and tinzaparin

B. Indications for Use

1. Similar to standard heparin (e.g., DVT/PE, ACS, DVT prophylaxis)
2. Used with increasing frequency as compared to standard heparin due to greater convenience (e.g., subcutaneous administration, less frequent monitoring) and decreased risk of side effects (e.g., HIT, osteoporosis)
3. More expensive than standard heparin, but often more cost-effective in the long run due to reduced testing, nursing time, and length of hospital stay
4. Preferred agent, along with direct oral anticoagulant agents (DOACs) in cancer-associated thrombosis

C. Contraindications

1. Similar to standard heparin (e.g., history of HIT type 2, active bleeding, severe thrombocytopenia)
2. Use with caution in patients with renal dysfunction—LMWH excreted via kidneys

Warfarin

A. Mechanism of Action

1. Inhibits action of vitamin K epoxide reductase, an enzyme required for the hepatic synthesis of vitamin K–dependent coagulation factors, leading to a decrease in factors II, VII, IX, X, and proteins C and S
2. Causes prolongation of PT (and increase in INR)
3. Anticoagulant effect begins after 4 to 5 days of use, requiring the use of a concurrent heparin "bridge" if immediate anticoagulation is required. Once warfarin is therapeutic (via INR monitoring), stop heparin and continue warfarin alone

B. Indications for Use

1. Thromboembolism prophylaxis (e.g., DVT/PE, stroke secondary to atrial fibrillation), although less often used than DOACs due to need for monitoring and titration
2. Preferred anticoagulant for patients with mechanical heart valves or antiphospholipid antibody syndrome

C. Administration

1. Given orally
2. Heparin must be initiated first to avoid warfarin-induced skin necrosis (see below)
3. Once PTT is therapeutic on heparin alone, initiate warfarin
4. Continue heparin for at least 4 days after starting warfarin
5. Once INR is therapeutic on warfarin, stop the heparin
6. Monitored via INR—in most cases, INR of 2 to 3 is therapeutic (patients with mechanical heart valves may have a higher goal INR such as 2.5 to 3.5)

D. Adverse Effects

1. Bleeding
2. Skin necrosis—rare but serious complication caused by rapid decrease in protein C (a vitamin K–dependent inhibitor of factors Va and VIIIa)

E. Contraindications

1. Active bleeding, severe coagulopathy or thrombocytopenia
2. Pregnancy—warfarin is a teratogen

F. Reversing the Effects of Warfarin

1. Discontinue warfarin—takes 5 days to correct due to the long half-life of warfarin
2. Treatment depends on degree of INR elevation and presence of bleeding or urgent surgery
3. Administer vitamin K—takes 12 to 24 hours to correct due to the time required for the liver to synthesize new clotting factors
4. Transfuse FFP—may take up to 8 hours to correct due to the time required for transfusion
5. Administer unactivated prothrombin-complex concentrates (PCCs)—replaces vitamin K–dependent coagulation factors and corrects within 10 minutes of administration

Quick HIT

If rapid reversal of acute bleeding from warfarin is indicated, give IV, vitamin K, FFP, and PCC.

Direct Oral Anticoagulants

A. Overview and Mechanism of Action

1. May also be referred to as novel oral anticoagulants (NOACs)
2. DOACs are more frequently used for VTE prophylaxis and treatment over heparin, LMWH, and vitamin K antagonists due to their ease of dosing and monitoring
3. Direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban)

a. Inhibit factor Xa directly (as opposed to potentiating AT III like heparin)
b. Currently approved for treatment of DVT/PE, DVT/PE prophylaxis, and stroke prophylaxis in patients with atrial fibrillation

4. Direct thrombin (factor II) inhibitors (e.g., dabigatran is the only oral direct thrombin inhibitor)
   a. Inhibit thrombin directly
   b. Parenteral forms of direct thrombin inhibitors include bivalirudin and argatroban (limited to inpatient use for acute coronary syndrome or treatment of HIT type 2)

B. Administration and Dosing Considerations

1. Dose adjustments for renal disease
   a. All DOACs are excreted renally to varying degrees
   b. Most will need dose reduction for CrCl 30 to 50 mL/min
   c. For CrCl <30 mL/min, there is emerging evidence that DOACs (apixaban) can be used safely, but more studies are needed
2. Considerations for choosing an agent
   a. Dabigatran and apixaban are twice-daily dosing
   b. Rivaroxaban and edoxaban are once daily
   c. Cost can be an issue

C. Advantages and Disadvantages

1. No injections are needed
2. Less laboratory monitoring is needed (heparin and warfarin both require monitoring) and no bridging required
3. Generally have lower intracranial bleeding risk than warfarin
4. Cost of DOACs is often higher than warfarin
5. Warfarin or heparin still preferred over DOACs for some situations:
   a. Mechanical prosthetic heart valve
   b. Pregnancy (less clinical experience with DOACs)
   c. Renal disease with CrCl <30 mL/min
   d. Advanced stage cirrhosis
   e. Antiphospholipid syndrome

Oncology

- A detailed description of many cancers can be found in the appropriate anatomical chapter of this book (i.e., lung cancers in pulmonary chapter, colon cancer in GI).

Epidemiology

- In order of occurrence, the most common cancers in males worldwide are lung, prostate, and colorectal. The cancer with the highest mortality in males is lung, followed by prostate and colon.
- In order of occurrence, the most common cancers in females worldwide are breast, colorectal, and lung. The cancer with the highest mortality in females is lung, followed by breast and colon.
- The number one avoidable risk factor for most cancers is smoking. All patients should be encouraged to stop smoking.
- Other etiologic agents in cancer include viruses (e.g., hepatitis B/C for hepatocellular carcinoma, HPV in cervical cancer), chemicals (e.g., asbestos, ethanol, aflatoxin, cadmium, silica), and UV light.

Cancer Prevention and Screening

- Breast cancer—mammogram every 2 years beginning at age 50 years for females (may start earlier at age 40 for those who opt to begin screening)
- Cervical cancer—HPV vaccine approved for all individuals ages 9 to 26 years; pap smears every 3 years for individuals with a cervix ages 21 to 30 years (even if not sexually active) and every 5 years with HPV co-testing for ages 30 to 65 years
- Colorectal cancer (CRC)—screening for average-risk individuals starting at age 45 years; if first-degree relative with CRC, begin screening at age 40 or 10 years before the age of diagnosis of relative (whichever is earlier). Method of screening and frequency depends on patient preference and risk/benefit discussion. Options include:
- Annual stool-based tests such as FIT or FOBT
- Colonoscopy every 10 years
- Flexible sigmoidoscopy every 5 years
- CT colonography every 5 years

- Prostate cancer—no consensus that screening with prostate-specific antigen (PSA) testing decreases mortality
- Lung cancer—screen any previous (within past 15 years) or current smoker with minimum 20 pack-year history ages 50 to 80 years using low-dose CT annually

Principles of Cancer Staging and Therapy

- Cancer is usually treated using three modalities: surgery, systemic therapy (chemotherapy and/or immunotherapy), radiation
- *Clinical* staging is usually performed by clinical examination and imaging techniques (PET, CT, MRI scans). TNM staging is most commonly employed:
- T (T1–T4) describes the size of the primary tumor and whether it has invaded any nearby tissue
- N (N1–N3) describes extent of tumor spread to regional lymph nodes
- M (M0 or M1) indicates presence or absence of any distant metastatic disease.
- *Pathologic* staging is defined after surgical resection and can give more precise information with regard to local or distant spread of the tumor

A. Surgical Oncology

1. Goal is to resect primary tumor with negative margins
2. Many times these surgeries involve excision or sampling of locoregional lymph nodes
3. Work closely with medical and radiation oncologists to determine optimal treatment plan based on accurate clinical staging and evidence-based medicine

B. Radiation Oncology

1. Basics of radiation therapy
   a. Therapy using ionizing radiation that is generated by either megavoltage linear accelerators, heavy ions (e.g., protons, neutrons, carbon ions), or radioisotopes (e.g., iodine-131 for thyroid cancer)

b. Can be given via an external beam (EBRT or stereotactic radiosurgery), sealed source that is implanted in or near a tumor (brachytherapy), or as a radiation source conjugated to antibodies (radioimmunotherapy)

2. Mechanism of action
   a. Photons interact with biologic matter and damage DNA either directly or indirectly (through generation of reactive oxygen species)
   b. DNA double-strand breaks are the critical determinant of cellular response to radiation and eventual cell death
3. Clinical radiation oncology
   a. Radiation is primarily used in conjunction with surgery as adjuvant therapy to prevent local tumor recurrence
   b. With the advent of new technologies that allow for dose escalation while sparing normal tissues, radiation can also be used as definitive therapy (e.g., stereotactic radiosurgery for inoperable brain tumors and early-stage lung cancers) or as neoadjuvant therapy (i.e., to shrink tumors prior to surgery)

C. Medical Oncology

1. Systemic therapy (chemotherapy and immunotherapy)
   a. Primarily used when cancer has spread regionally or systemically
   b. Also used in the adjuvant setting (to prevent tumor recurrence) and neoadjuvant setting (to decrease size of tumor prior to resection)
   c. Chemotherapy is definitive therapy for most leukemias and can be used to consolidate disease or induce a remission
2. Mechanisms of action
   a. A comprehensive list of chemotherapeutic agents is too vast to be covered in this section, but key categories include DNA alkylating agents (e.g., melphalan, cyclophosphamide, cisplatin, carboplatin), antimetabolites (e.g., methotrexate, cytarabine, gemcitabine, fluorouracil), antimicrotubule agents (e.g., vincristine, paclitaxel, docetaxel), topoisomerase inhibitors (e.g., irinotecan, topotecan), and anthracyclines (e.g., doxorubicin, daunorubicin, bleomycin)
   b. Next-generation systemic agents
      - Targeted therapies interfere with specific mutations that give rise to cancer—examples include imatinib (targets the tyrosine kinase

that is aberrantly upregulated in the majority of chronic myelogenous leukemias), trastuzumab (blocks HER2/neu receptor in breast cancers with amplification of this oncogene), and cetuximab (epidermal growth factor receptor inhibitor)

- Immunotherapy agents target various immune system checkpoints —examples include nivolumab and pembrolizumab (PD-1 receptor inhibitors), atezolizumab (PD-L1 inhibitor)
- Checkpoint inhibitor immunotherapy agents are becoming more widely used. Similar to chemotherapy agents, they have a wide range of immune-related adverse events (irAEs):
  - Cytokine release syndrome (especially with chimeric antigen receptor (CAR)-T cell therapy
  - Inflammation of multiple organ systems including: dermatitis, vasculitis, hepatitis, colitis, pneumonitis, and endocrinopathies (hypo/hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes)

Quick HIT

Oncologic emergencies which necessitate immediate treatment include hypercalcemia (IV fluids, bisphosphonates, denosumab), spinal cord compression (steroids, MRI, surgical consult), pericardial tamponade (pericardiocentesis), and tumor lysis syndrome (IV fluids, urate lowering therapy, correction of electrolyte abnormalities).

Breast Cancer

A. Risk factors include prior history of breast cancer, age, family history of breast cancer, female gender, prior thoracic radiation, smoking, alcohol

consumption, and anything which increases the number of menstrual cycles (early menarche, late menopause, nulliparity).

B. Breast cancer is rare in women under 35 years—think of fibroadenoma if a young woman presents with a round, movable mass which changes in size over the course of the menstrual cycle.

C. The differential diagnosis for a breast mass at any age includes cysts (benign if not bloody after aspiration and does not recur) and fibrocystic changes (bilateral breast pain caused by cyclic hormonal stimulation).

D. The premalignant in situ breast cancers are ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS)—distinguished histologically:

1. DCIS represents a broad spectrum of disease which arises from the ductal elements of the breast. It is often found on screening mammogram, and a mass may or may not be present. As this is a marker for the possible development of invasive ductal carcinoma (typically in the same breast), treat with lumpectomy (or mastectomy if negative margins cannot be achieved). Radiation and systemic chemotherapy are used less often depending on the specific lesion in question.
2. LCIS arises from the lobular elements of the breast. The lesion is typically found incidentally during biopsy of another breast lesion, and a mass is rarely palpable. It leads to an increased risk of breast cancer in either breast. Unfortunately, removal of the lesion does not reduce the risk of progression to invasive cancer. Treatment is variable, but may include close observation, selective estrogen receptor modulators, and prophylactic bilateral mastectomy.

E. The two most common types of breast cancer are infiltrating ductal carcinoma, accounting for over 70% of invasive breast cancers, and infiltrating lobular carcinoma.

1. Patients may present with a palpable mass, palpable lymph nodes, skin dimpling, nipple retraction, or no symptoms at all (found on mammogram).

2. Diagnosis should be confirmed with tissue biopsy, which should include testing for the estrogen/progesterone receptor and HER-2/neu amplification status.
3. Treatment typically begins with surgery with adjuvant radiotherapy (if the tumor has not spread to sentinel lymph nodes) to decrease tumor recurrence.
4. Adjuvant chemotherapy is required for large lesions in premenopausal women, but is typically not necessary for all small lesions (typically <1 cm) without lymph node involvement.
5. Postmenopausal women with large lesions or lymph node involvement may receive either chemotherapy or an aromatase inhibitor (anastrozole, letrozole), depending on the status of the estrogen receptor. Tamoxifen may be used as an alternate agent for those who cannot tolerate an aromatase inhibitor.

Plasma Cell Disorders

Monoclonal Gammopathy of Undetermined Significance

- Common in the elderly (over 5% in patients >70 years of age)
- Asymptomatic, premalignant clonal plasma cell proliferation
- Diagnosis is confirmed by the presence of monoclonal protein (M-protein) spike <3.0 g/dL and <10% plasma cells in bone marrow *without* evidence of multiple myeloma (i.e., lytic bone lesions, anemia, hypercalcemia, or renal insufficiency)
- About 1% of people with MGUS will develop multiple myeloma each year. Patients can be risk stratified by multiple laboratory parameters
- No specific treatment is necessary (just close observation)

Multiple Myeloma

A. General Characteristics

1. Multiple myeloma is characterized by the neoplastic proliferation of a single plasma cell line that produces monoclonal immunoglobulin, leading to enormous copies of one specific immunoglobulin (usually of the IgG or IgA type)
2. Median age at diagnosis is 65 to 75 years and is more frequent in men than in women. Higher prevalence in Black populations than in White populations, although not well studied in other populations.
3. The etiology is unclear, but associated risk factors include elevated BMI and Agent Orange exposure
4. As the disease process advances, bone marrow elements are replaced by malignant plasma cells, resulting in anemia, leukopenia, and thrombocytopenia

***Quick* HIT**

The signs of multiple myeloma can be remembered using the mnemonic CRAB: **C**alcium (hypercalcemia), **R**enal failure, **A**nemia, and **B**one lesions (lytic)

***Quick* HIT**

Diagnostic criteria for multiple myeloma include at least 10% abnormal plasma cells in bone marrow *plus* one of the following:
- M-protein in the serum
- M-protein in the urine
- Lytic bone lesions (well-defined radiolucencies on radiographs)

B. Clinical Features

1. Lytic bone lesions—result in significant bone pain (especially in the low back, chest, and jaw), pathologic fractures, and loss of height secondary to collapse of vertebrae
2. Anemia—present in most patients due to bone marrow infiltration and renal failure

3. Renal failure—due to myeloma nephrosis (immunoglobulin precipitation in renal tubules) and hypercalcemia
4. Recurrent infections (especially of the lung or urinary tract)—most common cause of death, due to lack of normal immunoglobulins
5. Cord compression—may occur secondary to a plasmacytoma or fractured bone fragment

Quick HIT

Almost all patients with multiple myeloma have an M-protein in either the serum or urine. However, some patients may have light chain myeloma or nonsecretory myeloma.

C. Diagnosis

1. Serum and urine protein electrophoresis (SPEP/UPEP) and immunofixation (IFE)—reveals monoclonal protein spike (M-spike) due to a malignant clone of plasma cells synthesizing a single Ig (usually IgG, although specific subtype can be determined via immunofixation)
2. Free light chain assay—measures kappa and lambda light immunoglobulin chain ratio. Most patients with multiple myeloma will have an elevated free light chain ratio
3. Low-dose CT, PET/CT, or MRI—reveal lytic bone lesions
4. Bone marrow biopsy (required for diagnosis)—reveals >10% abnormal plasma cells
5. Hypercalcemia—due to bone destruction
6. Elevated serum total protein—due to paraproteins in blood (hyperglobulinemia)
7. Elevated creatinine—due to renal damage
8. Anemia, leukopenia, or thrombocytopenia (especially in advanced disease)—due to bone marrow invasion
9. Peripheral blood smear—reveals normocytic anemia with RBCs in rouleaux formation (RBCs resemble a stack of poker chips as a result of clumping caused by hyperglobulinemia) (Figure 9-12)
10. Urinalysis—Bence Jones proteins will not be detected on urine dipstick which only detects albumin (urine protein is usually negative),

but urine microscopy can reveal myeloma casts (large, waxy laminated casts)

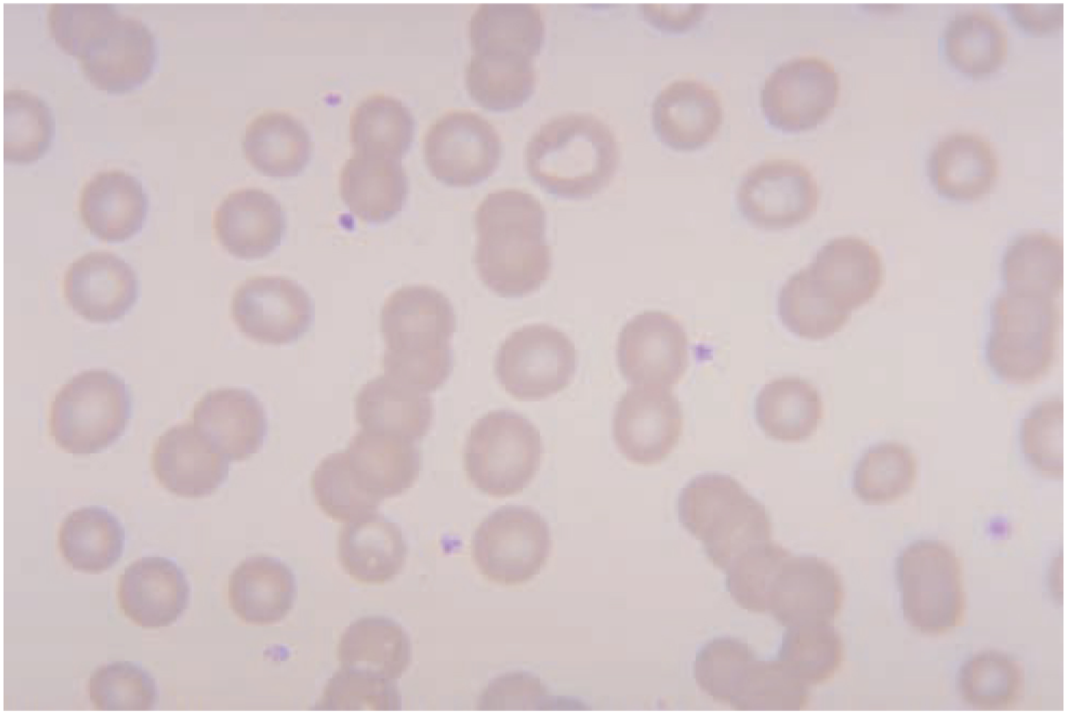


FIGURE 9-12 **Rouleaux formation (multiple myeloma).** (Reprinted with permission from Anderson SC, Poulsen KB. *Anderson's Atlas of Hematology*. Lippincott Williams & Wilkins; 2003.)

***Quick* HIT**

- Radiographs show punched-out lytic lesions, osteoporosis, or fractures in 75% of patients with multiple myeloma
- Osteolytic lesions are secondary to the release of osteoclast-activating factor by the neoplastic plasma cells

D. Treatment

1. In contrast to the premalignant conditions MGUS and smoldering multiple myeloma, patients with MM and end-organ damage require treatment
2. The preferred treatment is high-dose chemotherapy for induction therapy, followed by autologous hematopoietic cell transplantation

(HCT)
3. Bisphosphonates for patients with one or more skeletal lesions

Quick HIT

Multiple myeloma has a variable prognosis depending on multiple features of disease and comorbidities. The 5-year survival rate is about 50%.

A 69-year-old woman presents with a 2-month history of worsening lower back pain, confusion, mild abdominal pain, weight loss, and constipation. She takes hydrochlorothiazide for hypertension and simvastatin for hypercholesterolemia. Physical examination is unremarkable and a stool fecal immunochemical test (FIT) is negative. Laboratory results are shown below. A peripheral blood smear demonstrates stacked red blood cells.

Leukocyte count	9,000/mm^3
Hemoglobin	9.1 g/dL
Platelets	290,000/mm^3
Blood urea nitrogen	32 mg/dL
Creatinine	2.1 mg/dL
Erythrocyte sedimentation rate	68 mm/h
Lipase	67 U/L

Which of the following additional findings do you expect with this patient’s condition?

A. Mechanical obstruction
B. Hypercalcemia
C. Pericarditis
D. Pancreatitis

- **The answer is B: Hypercalcemia.** The patient in this question is presenting with anemia, low back pain, increased erythrocyte sedimentation rate (ESR), and renal dysfunction, suggesting the diagnosis of multiple myeloma. The peripheral smear shows the rouleaux formation (stacked appearance of RBCs), which may also be seen in this condition. In addition, the patient is presenting with constipation and confusion, both symptoms of hypercalcemia (>10.2 mg/dL), which is seen in about one-third of patients with multiple myeloma (however, this patient is also on a thiazide diuretic which

may be worsening the hypercalcemia). The etiology of hypercalcemia in multiple myeloma is bone lysis from humoral factors released by the plasma cells. **(A)** Mechanical obstruction secondary to malignancy also can cause constipation, but the patient's signs and symptoms do not suggest colon cancer. **(C, D)** Pericarditis is not associated, and the normal lipase argues against pancreatitis causing this patient's symptoms.

***Quick* HIT**

Hyperviscosity syndrome can lead to retinal vessel dilation with resulting hemorrhage and possible blindness.

***Quick* HIT**

- Lymphomas are cancers of the lymphatic system
- There are two types: Hodgkin disease and non-Hodgkin disease (NHL)
- Lymphadenopathy is usually the first finding in lymphomas

Waldenström Macroglobulinemia

- Malignant proliferation of plasmacytoid lymphocytes that produce IgM paraprotein, a very large protein that causes hyperviscosity of the blood
- Diagnosis is confirmed by the presence of an IgM monoclonal gammopathy and ≥10% plasmacytoid lymphocytes on bone marrow biopsy
- Clinical features include fatigue, weight loss, neurologic symptoms, lymphadenopathy, splenomegaly, anemia, abnormal bleeding, Bence Jones proteinuria, and hyperviscosity syndrome (due to elevated IgM, which can cause neurologic symptoms ranging from blurry vision and headache to stroke or coma)
- There is no definitive cure—use rituximab plus chemotherapy and plasmapheresis for hyperviscosity syndromes

Lymphomas

Hodgkin Lymphoma

A. General Characteristics

1. Bimodal age distribution: X_1 = 15 to 30 years of age; X_2 = >50 years of age
2. Lymph node histology divides the disease into four subtypes:
   a. Lymphocyte predominance (5%)—few Reed–Sternberg cells and many B cells
   b. Nodular sclerosis (70%)—occurs more frequently in women; bands of collagen envelope pools of Reed–Sternberg cells
   c. Mixed cellularity (25%)—large numbers of Reed–Sternberg cells in a pleomorphic background
   d. Lymphocyte depletion (<1%)—lacking in mix of reactive cells; associated with the worst prognosis
3. Staging is based on physical examination, CT scan (chest, abdomen, pelvis), and bone marrow biopsy. Ann Arbor staging system:
   a. Stages
      - Stage I: confined to single lymph node (or one extralymphatic site)
      - Stage II: involvement of two or more lymph nodes but confined to same side of diaphragm
      - Stage III: both sides of diaphragm involved
      - Stage IV: dissemination of disease to extralymphatic sites
   b. Suffixes
      - A: No symptoms
      - B: Fever, weight loss, night sweats—presence of these constitutional symptoms worsens the prognosis

Quick HIT

The histologic subtype does not greatly influence the prognosis of Hodgkin disease (with the exception of the lymphocyte-depleted type, which has the worst prognosis). Treatment is effective in most patients with the other histologic types of Hodgkin disease.

Quick HIT

Chemotherapy and radiation therapy in combination achieve cure rates of over 70% in Hodgkin disease.

Quick HIT

Key Epidemiologic Associations With NHL

- Burkitt lymphoma endemic to regions of Africa
- Patients with HIV and HIV-associated lymphomas
- Adult T-cell lymphoma in Japan and the Caribbean

B. Clinical Features

1. Painless lymphadenopathy—most common symptom
   a. May involve supraclavicular, cervical, axillary, or mediastinal lymph nodes
   b. Spreads by continuity from one lymph node to adjacent nodes
2. B symptoms (e.g., fever, night sweats, weight loss)
3. Pruritus
4. Cough—secondary to mediastinal lymph node involvement

Quick HIT

It is beyond the scope of this chapter to give a detailed account of each specific type of NHL. Focus on the general clinical presentations as well as certain commonly tested pathologic features (see highlighted points in Table 9-6).

C. Diagnosis

1. Lymph node excisional biopsy
   a. Reveals Reed–Sternberg cells—required to make the diagnosis (Figure 9-13)
      - Large, neoplastic cell with two or more nuclei—resemble owl's eyes
      - Usually B-cell phenotype
      - May be found in other neoplasms

   b. Reveals inflammatory cell infiltrates—distinguishes Hodgkin lymphoma from NHL
      - The inflammatory cells present are reactive to the Reed–Sternberg cells
      - These include plasma cells, eosinophils, fibroblasts, and T and B lymphocytes
2. CXR and CT scan (chest, abdomen)—may reveal mediastinal mass or lymph node involvement
3. Bone marrow biopsy—may reveal bone marrow involvement
4. Leukocytosis with eosinophilia

Quick HIT

Rituximab, a monoclonal antibody against CD20 antigen, is often used in combination with CHOP therapy to treat NHL and other cancers with better outcomes than CHOP alone.

Quick HIT

Staging NHL

- Stage I: single lymph node involved (or one extralymphatic site)
- Stage II: two or more lymph nodes on the same side of the diaphragm
- Stage III: lymph node involvement on both sides of the diaphragm
- Stage IV: disseminated involvement of one or more extralymphatic organs with or without lymph node involvement

D. Treatment

1. Consists mainly of chemotherapy and radiation therapy to the involved field
2. Stages I and II are usually treated with a combination of chemotherapy and radiation, although chemotherapy alone may be acceptable for some patients
3. Stages IIIB and IV require combination chemotherapy

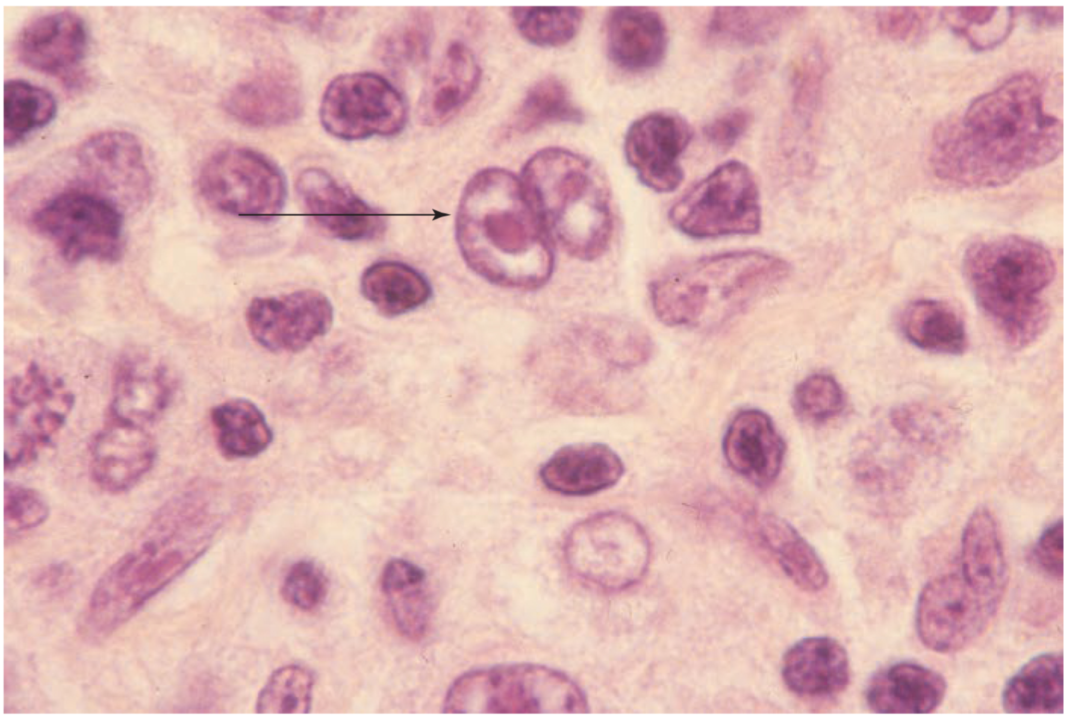


FIGURE 9-13 **Reed–Sternberg cells (Hodgkin lymphoma).** (Reprinted with permission from Anderson SC, Poulsen KB. *Anderson's Atlas of Hematology*. Lippincott Williams & Wilkins; 2003.)

Non-Hodgkin Lymphoma

A. General Characteristics

1. NHL is a diverse group of solid tumors which occurs with the malignant transformation and growth of B or T lymphocytes (or their precursors) in the lymphatic system

   a. The type of lymphocyte involved and its level of differentiation determine the course of the disease and its prognosis
   b. B-cell lymphomas account for 85% of all cases, while T-cell lymphomas account for 15% of all cases
   c. The disease usually starts in lymph nodes and may spread to blood and bone marrow
2. NHL is the ninth most common cause of cancer-related death in the United States
3. NHL is twice as common as Hodgkin disease, and patients with NHL tend to have more advanced disease at presentation than patients with Hodgkin disease
4. The mean age of onset varies with subtype, but there is an increased overall incidence with increasing age
5. Risk factors
   a. HIV/AIDS
   b. Immunosuppression (e.g., organ transplant recipients)
   c. History of certain viral infections (e.g., EBV, HTLV-1)
   d. History of *Helicobacter pylori* gastritis (risk of primary associated gastric lymphoma)
   e. Autoimmune disease (e.g., Hashimoto thyroiditis or Sjögren syndrome [risk of mucosa-associated lymphoid tissue])
6. Classification
   a. There are more than 20 different subtypes of NHL, arranged into several unique classification systems
   b. One such classification system stratifies subtypes according to histologic grade: low grade (or indolent), intermediate grade, and high grade (see Table 9-6)

B. Clinical Features

1. Painless lymphadenopathy—sometimes the only manifestation of disease
   a. Lymph nodes are usually firm and mobile
   b. Most often involves supraclavicular, cervical, and axillary nodes
2. B symptoms—less common than in Hodgkin lymphoma
3. Hepatosplenomegaly

4. Primary GI lymphoma may present with anorexia, vomiting, early satiety, bowel obstruction, or weight loss
5. Progressive rash (cutaneous lymphoma)
6. Anemia, leukopenia, or thrombocytopenia—due to bone marrow involvement

TABLE 9-6 Non-Hodgkin Lymphomas

Grade[a]	Type[a]	Key Features	Prognosis
Indolent or Low Grade	Small lymphocytic lymphoma	• **Closely related to CLL;** more common in elderly patients • **Indolent course**	• Eventually results in widespread lymph node involvement with dissemination to liver, spleen, and bone marrow
	Follicular, predominantly small, cleaved-cell lymphoma	• **Most common form of NHL** • Mean age of onset is 55 yrs • May transform into diffuse, large cell; associated with translocation: t(14;18) • Indolent course • **Presents with painless, peripheral lymphadenopathy**	• Most patients with localized disease can be cured with radiotherapy, but only 15% of patients do have localized disease • Median survival is approximately 10 yrs
Intermediate	Diffuse, large-cell lymphoma	• Predominantly B-cell origin • Middle-aged and elderly patients • **Locally invasive; presents as large extranodal mass**	• 85% cure rate with CHOP therapy
High Grade	Lymphoblastic lymphoma	• **T-cell lymphoma;** more common in children • **May progress to T-ALL** • 50% of patients have B symptoms	• **Aggressive with rapid dissemination,** but may respond to combination chemotherapy
	Burkitt (small noncleaved-cell) lymphoma	• **B-cell lymphoma;** more common in children • Two types: African and American; the African variety involves facial bone and jaw, whereas the American variety often involves abdominal organs (hepatomegaly, abdominal masses, lymphadenopathy) • **African variety linked with EBV infection**	• Grave prognosis unless treated very aggressively with chemotherapy • Treatment may cure 50–60% of patients

		• **Associated with specific translocation: t(8;14)**	
Miscellaneous Lymphomas	Mycosis fungoides	• T-cell lymphoma of the skin • Presents with **eczematoid skin lesions** that progress to generalized erythroderma • **Cribriform shape of lymphocytes** • Disseminate to lymph nodes, blood, and other organs	• Depends on degree of dissemination (<2 yrs if dissemination has occurred) • Potentially curable (with radiation, topical chemotherapy) if limited to skin
	Sézary syndrome	Involves skin as well as blood stream	
	HIV-associated lymphomas	Not a discrete entity: usually Burkitt or diffuse, large-cell lymphoma	• Very poor prognosis

[a]Not all types for each grade are included in this table.

Quick HIT

- Prognosis varies significantly by subtype but can be estimated using the international prognostic index for non-Hodgkin lymphoma
- For all non-Hodgkin lymphomas, 5-year survival is around 65%
- In general, high-grade lymphomas (like diffuse large B-cell lymphoma) require more intensive treatment but often respond well to treatment

C. Diagnosis

1. Lymph node excisional biopsy—any lymph node >1 cm present for more than 4 weeks that cannot be attributed to infection should be biopsied
2. CXR and CT scan (chest, abdomen, pelvis)—may reveal lymph node involvement
3. Bone marrow biopsy—may reveal bone marrow involvement
4. Lumbar puncture may be needed for suspected leptomeningeal metastases or CNS lymphoma
5. Elevated alkaline phosphatase if bone or liver involvement
6. Elevated liver function tests or bilirubin if liver involvement

7. Anemia, leukopenia, or thrombocytopenia if bone marrow involvement

Quick HIT

CHOP therapy consists of:
- **C**yclophosphamide
- **H**ydroxydaunomycin (doxorubicin)
- **O**ncovin (vincristine)
- **P**rednisone

D. Treatment

1. Varies depending on the stage and subtype of NHL
2. Indolent forms of NHL are rarely curable, but have a 5-year survival rate of 75%. These patients are treated in a variety of ways, including observation, chemotherapy, and radiation therapy.
3. Intermediate and high-grade NHLs may be curable with aggressive treatments, but if complete remission is not achieved, survival is usually less than 2 years. In general, aggressive forms are treated with multiple regimens of combination chemotherapy (e.g., CHOP) and radiation therapy.
4. Some patients may benefit from high-dose chemotherapy with bone marrow transplantation.

Quick HIT

Acute leukemias account for 60% of all leukemias, 25% are CLL and 15% are CML.

Quick HIT

General Evaluation in Patients With Leukemias (acute or chronic)

- Evidence of infection
- Evidence of bleeding or easy bruising
- Lymphadenopathy, hepatosplenomegaly
- Signs of anemia
- Fatigue, weight loss

Quick HIT

For testing purposes, the age of a patient can be a simple yet important aid to confirming the correct leukemia diagnosis. Patients less than 15 most likely have ALL, while those greater than 65 typically have CLL. AML and CML both typically present from ages 40 to 60 years.

Leukemias

Acute Leukemias

A. General Characteristics

1. Two types
   a. Acute myelogenous leukemia (AML)
      - Neoplasm of myelogenous progenitor cells
      - AML occurs mostly in adults (accounts for 80% of adult acute leukemias)
      - Risk factors include exposure to radiation, myeloproliferative syndromes, Down syndrome, and prior chemotherapy (e.g., alkylating agents)
      - Response to therapy is not as favorable as in acute lymphoblastic leukemia
      - Poor prognostic indicators include older age, presence of other medical comorbidities, and history of exposure to cytotoxic agents and/or radiation therapy

- One important variant of AML is APL. This condition is characterized by **t(15;17)** and often presents with pancytopenia. Patients may be very sick, so treatment should be started with all-trans retinoic acid (ATRA) without delay along with concurrent chemotherapy once the diagnosis is confirmed (see Clinical Pearl 9-5)

b. Acute lymphoblastic leukemia (ALL)

- Neoplasm of early lymphocytic progenitor cells—histology reveals a predominance of lymphoblasts
- ALL is the most common malignancy in children under age 15 in the United States
- It is the leukemia most responsive to therapy
- Poor prognostic indicators include age <2 or >9, WBC $>10^5/mm^3$, and/or CNS involvement
- Presence of any of the following is associated with an increased risk for CNS involvement: B-cell phenotype, increased LDH, rapid leukemic cell proliferation

2. Many patients with acute leukemias can be cured if treated aggressively. If left untreated, the most aggressive acute leukemias can be fatal within months

CLINICAL PEARL 9-5

Leukemias

- Leukemias are characterized by neoplastic proliferation of abnormal WBCs. As these abnormal WBCs accumulate, they interfere with the production of normal WBCs, as well as the production of erythrocytes and platelets, resulting in anemia and thrombocytopenia.
- Leukemias are classified in two ways:
  - By the type of WBC affected
  - If granulocytes or monocytes are affected, myelogenous leukemia is present
  - If lymphocytes are affected, lymphocytic leukemia is present
- By the maturity of cells affected and the rapidity of disease progression
  - Acute leukemias are characterized by rapid progression and affect immature cells (i.e., immature cells proliferate before maturation)
  - Chronic leukemias progress slowly and affect mature cells

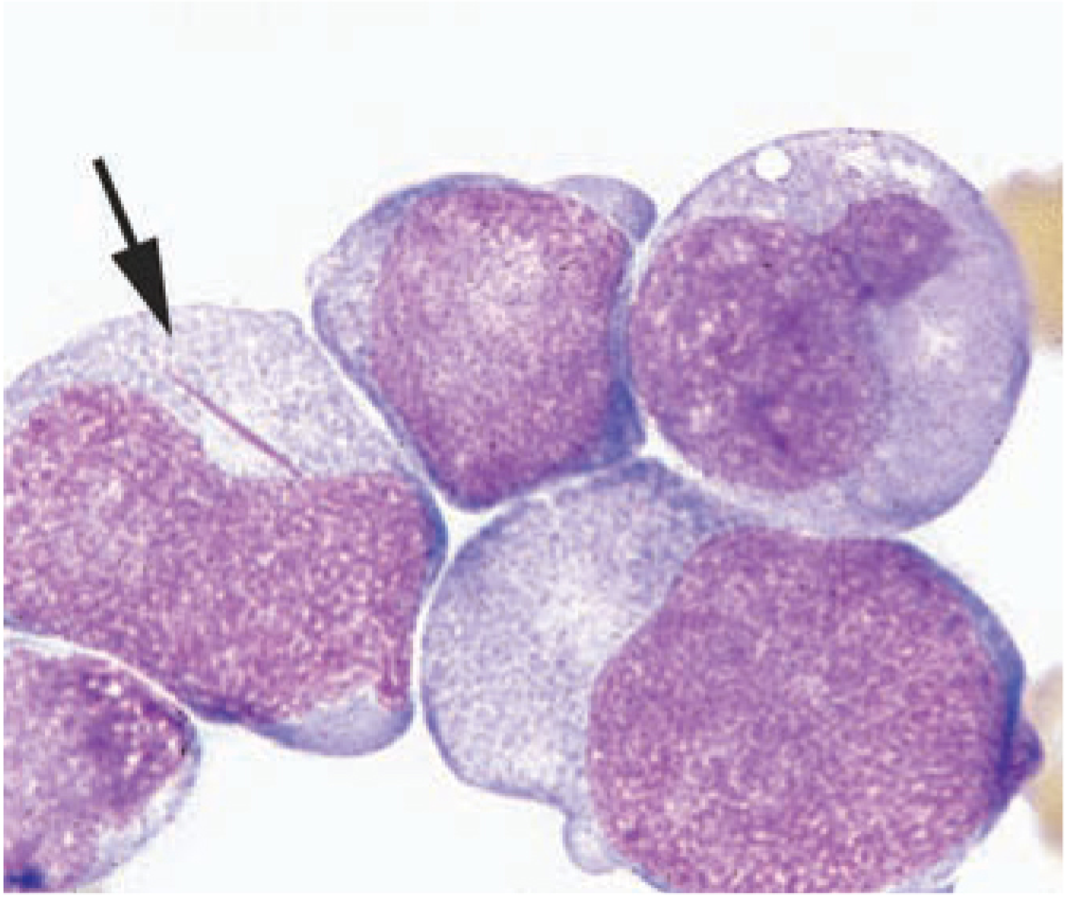


FIGURE 9-14 **Auer rod (acute myelogenous leukemia).** (Reprinted with permission from Sabatine MS. *Pocket Medicine*. 7th ed. Wolters Kluwer; 2019.)

B. Clinical Features

1. Anemia and its associated signs/symptoms (e.g., dyspnea, pallor)
2. Increased risk of bacterial infections—due to neutropenia
   a. Pneumonia, urinary tract infection, cellulitis, pharyngitis, esophagitis
   b. Associated with high morbidity and mortality (potentially life-threatening)
3. Thrombocytopenia and associated signs/symptoms (e.g., epistaxis, bleeding at puncture sites, petechiae/purpura, ecchymoses). APL in particular has a high risk of DIC
4. Splenomegaly, hepatomegaly, lymphadenopathy
5. Bone and joint pain—due to invasion of periosteum
6. Diffuse or focal neurologic dysfunction (e.g., meningitis, seizures)—due to CNS involvement

7. Testicular involvement (ALL)
8. Anterior mediastinal mass (T-cell ALL)
9. Skin nodules (AML)

Quick HIT

Auer rods (granules and eosinophilic rods inside malignant cells) are present in AML but not ALL.

Quick HIT

Tumor Lysis Syndrome (TLS)

- This is a potential complication of chemotherapy seen in acute leukemia, high-grade NHL, and solid cancers with very high tumor burden. TLS can occur spontaneously with leukemia.
- Rapid cell death with release of intracellular contents causes hyperkalemia, hyperphosphatemia, and hyperuricemia
- Treat as a medical emergency with aggressive IV hydration and urate lowering therapy

C. Diagnosis

1. Leukopenia or leukocytosis—WBC count is variable (from 1,000/mm^3 to 100,000/mm^3), but always accompanied by significant numbers of blast cells (immature cells) in peripheral blood
2. Anemia
3. Thrombocytopenia
4. Electrolyte disturbances (e.g., hyperuricemia, hyperkalemia, hyperphosphatemia) in tumor lysis syndrome
5. Bone marrow biopsy (required for diagnosis)
   a. In ALL, reveals proliferation of blasts of the lymphoid lineage (>20%)
   b. In AML, reveals proliferation of blasts of the myeloid lineage (>20%) and Auer rods, especially if it is the APL phenotype (Figure 9-14)

A patient being treated with combination chemotherapy for acute lymphoblastic leukemia (ALL) is noted to have increased levels of blood urea nitrogen (BUN) and creatinine on day 4 of treatment. The patient is immediately started on intravenous fluids. An ECG is ordered which demonstrates a prolonged QT interval. For confirmation of the diagnosis, several laboratory tests, including a complete metabolic profile, are ordered.

Which of the following laboratory abnormalities result from this patient's condition?

A. Decreased calcium, increased phosphate, decreased uric acid, decreased potassium
B. Decreased calcium, increased phosphate, increased uric acid, increased potassium
C. Decreased calcium, decreased phosphate, increased uric acid, increased potassium
D. Increased calcium, increased phosphate, increased potassium, increased uric acid

- **The answer is B: Decreased calcium, increased phosphate, increased uric acid, increased potassium.** Tumor lysis syndrome is associated with tumors with high cell turnovers. Lab findings include hypocalcemia (as evidenced by the patient's prolonged QT interval), hyperphosphatemia, hyperkalemia, and hyperuricemia. Hyperphosphatemia and hyperkalemia result since both potassium and phosphate are intracellular ions, which are released after cell lysis. The subsequent increase in phosphate levels binds calcium and causes hypocalcemia. Uric acid elevation occurs due to degradation of cellular proteins. Tumor lysis syndrome can cause acute renal failure (as seen with this patient) and fatal arrhythmias.

D. Treatment

1. Treatment of emergencies

   a. Antibiotics as necessary for infection
   b. Blood transfusion as necessary for anemia
   c. Platelet transfusion as necessary for bleeding
2. Aggressive, combination chemotherapy in high doses for several weeks is appropriate to obtain remission (i.e., absent leukemic cells in bone marrow). Once remission occurs, maintenance therapy is used for months or years to prevent recurrence.
   a. ALL: More than 75% of children with ALL achieve complete remission (compared with 30% to 40% of adults). Relapses, when they occur, usually respond to treatment. With aggressive therapy, survival rates in children can be up to 15 years or longer. Up to 50% of patients are cured
   b. AML: This is more difficult to treat and does not respond as well to chemotherapy. Survival rates are considerably lower despite intensive treatment. Bone marrow transplantation gives the best chance of remission or cure
3. Bone marrow transplantation

Chronic Lymphocytic Leukemia

A. General Characteristics

1. CLL is the most common leukemia among adults in the Western world, and the most common leukemia that occurs after age 50. Most patients with CLL are >60 years of age.
2. Caused by the monoclonal proliferation of lymphocytes that are morphologically mature but functionally defective (i.e., they do not differentiate into antibody-manufacturing plasma cells).
3. In general, this is the least aggressive type of leukemia, and CLL patients survive longer than those with acute leukemias or chronic myeloid leukemia (CML). The natural history is variable, but may follow a prolonged indolent course. Many patients die of other causes.
4. The most recent WHO classification describes CLL as identical to the indolent NHL B-cell neoplasm small lymphocytic leukemia (SLL). They are considered the same disease at different stages.

B. Clinical Features

1. Usually asymptomatic at time of diagnosis—may be discovered secondary to abnormalities on routine labs
2. Painless lymphadenopathy (usually cervical)
3. Hepatosplenomegaly
4. Frequent respiratory or skin infections—due to immune deficiency
5. In more advanced disease: fatigue, weight loss, pallor, skin rashes, easy bruising, bone tenderness, and/or abdominal pain

Quick HIT

AIHAs can be seen in patients with CML.

C. Diagnosis

1. Lymphocytosis—WBC typically 50,000 to 200,000
2. Anemia
3. Thrombocytopenia
4. Neutropenia
5. Peripheral blood smear
   a. Reveals absolute lymphocytosis—almost entirely mature, small lymphocytes
   b. Reveals smudge cells—“fragile” leukemic cells that rupture when placed on glass slide
6. Flow cytometry—reveals clonal population of B cells
7. Bone marrow biopsy—reveals presence of infiltrating leukemic cells in bone marrow

Quick HIT

Remember that the cells of the myeloid lineage include erythrocytes, granulocytes, and platelets.

D. Treatment

1. Patients with asymptomatic disease are typically observed

2. Regimens for symptomatic CLL vary with the age of the patient: younger patients often receive a combination of fludarabine and rituximab, while older patients typically receive ibrutinib (an inhibitor of Bruton tyrosine kinase)
3. Prognosis is variable depending on the number of lymphoid tissues involved and the presence or absence of anemia/thrombocytopenia

Quick HIT

Differentiating Benign Leukemoid Reaction From CML Leukemoid Reaction

- Usually no splenomegaly
- Increased leukocyte alkaline phosphatase
- History of a precipitating event (e.g., infection)

Chronic Myeloid Leukemia

A. General Characteristics

1. Neoplastic, clonal proliferation of myeloid stem cells
2. Median age at presentation is around 50 years
3. Only known risk factor is exposure to ionizing radiation
4. CML follows an indolent (chronic) course for many years before it transforms to acute leukemia. The end-stage of the disease course is usually an acute phase (also known as a blast crisis), which is an accelerated phase of blast and promyelocyte production
5. It is associated with translocation t(9;22) in >90% of patients. This fusion of the BCR gene on chromosome 22 with the ABL1 gene on chromosome 9 is known as the Philadelphia chromosome. The abnormal chromosome results in a constitutively active tyrosine kinase protein, which is targeted by imatinib. Note that patients without the Philadelphia chromosome have shorter survival times and respond more poorly to treatment

Quick HIT

Treat CML with TKIs (e.g., imatinib, dasatinib, or nilotinib).

B. Clinical Features

1. Most patients (85%) present in the chronic phase and may be asymptomatic at the time of diagnosis—disease discovered on routine labs
2. Constitutional symptoms (e.g., fevers, night sweats, anorexia, weight loss)
3. Recurrent infections
4. Anemia and its associated signs/symptoms
5. Thrombocytopenia and its associated signs/symptoms
6. Hepatosplenomegaly
7. Lymphadenopathy
8. Patients may also present in more advanced stages (i.e., the accelerated phase or blast crisis)

Quick HIT

Tyrosine kinase inhibitors are current standard of care for CML.

C. Diagnosis

1. Leukocytosis with eosinophilia—WBCs from 50,000 to 200,000
2. Thrombocytosis
3. Peripheral blood smear—reveals increased numbers of immature granulocytes, anemia, thrombocytosis, and basophilia
4. Bone marrow biopsy—increased numbers of immature granulocytes

D. Treatment

1. Treatment for CML is one of the great stories of modern medicine. After the mechanism of disease was elucidated, the oral tyrosine kinase inhibitor (TKI) imatinib was developed. This drug targets the dysfunctional chimeric protein BCR-ABL formed by the t(9;22) Philadelphia chromosome. Second-generation TKIs are now available.

2. Unfortunately, patients who present in a blast crisis still have very poor outcomes. The TKIs can still be attempted in these patients. Stem cell transplantation is also an option.

Myeloproliferative Disorders

Polycythemia Vera

A. General Characteristics

1. Malignant clonal proliferation of hematopoietic stem cells leading to excessive erythrocyte production
2. The increase in RBC mass occurs independent of erythropoietin
3. The median survival with treatment is about 9 to 14 years
4. Mutations in the JAK2 tyrosine kinase are found in >90% of cases

> ***Quick* HIT**
>
> An often-tested presentation for PV is a patient who complains of severe pruritus after a hot bath or shower.

B. Clinical Features

1. Signs/symptoms of hyperviscosity: headache, dizziness, weakness, transient visual disturbances, dyspnea
2. Thrombosis (e.g., DVT, PE, stroke, MI, portal vein thrombosis)
3. Aquagenic pruritus (pruritus following a warm bath or shower)
4. Facial plethora
5. Hepatosplenomegaly
6. HTN

C. Diagnosis

1. Rule out causes of secondary polycythemia (e.g., hypoxemia, smoking, carbon monoxide exposure)
2. Elevated RBC count, Hb, Hct (usually >50%)

3. Thrombocytosis
4. Leukocytosis
5. Decreased serum erythropoietin levels
6. Hyperuricemia
7. Bone marrow biopsy—reveals hypercellularity with increased proliferation of erythrocyte, granulocyte, and megakaryocyte precursors
8. Peripheral blood scree for JAK2 mutation

Quick HIT

Diagnostic Criteria for Polycythemia Vera

Must have all three major criteria or the first two major criteria plus any two minor criteria:

Major Criteria

- Elevated Hb (men >16.5 g/dL; women >16.0 g/dL)
- Bone marrow biopsy with trilineage hypercellularity (erythroid, granulocytic, and megakaryocytic proliferation)
- *JAK2 V617F* or *JAK2* exon 12 mutation

Minor Criteria

- Serum erythropoietin level below normal

D. Treatment

1. Therapeutic phlebotomy—mainstay of therapy to lower hematocrit
2. Aspirin
3. Cytoreductive agents: hydroxyurea for patients with history of thrombosis

Myelodysplastic Syndromes

A. General Characteristics

1. Myelodysplastic syndromes are a class of acquired malignant hematopoietic stem cell disorders characterized by ineffective hematopoiesis.

2. The result is pancytopenia, despite a normal or hypercellular bone marrow.
3. They occur more commonly in elderly patients and are slightly more common in men.
4. They are usually idiopathic, although exposure to radiation, immunosuppressive agents, and certain toxins are known risk factors.
5. They are classified into subtypes according to findings on bone marrow biopsy and peripheral blood smear.
6. The prognosis, although variable, is generally poor, and the end result is often progression to acute leukemia.

Quick HIT

Hyperviscosity and elevated total blood volume in polycythemia vera account for most of the clinical findings.

B. Clinical Features

1. Often asymptomatic in the early stages—pancytopenia may be an incidental finding on routine labs
2. Anemia
3. Thrombocytopenia
4. Neutropenia—which often presents with infections
5. Autoimmune conditions are commonly present (rheumatoid arthritis, rheumatic heart disease, pernicious anemia, etc.)
6. Skin lesions (can present with acute febrile neutrophilic dermatosis or Sweet syndrome)

Quick HIT

Thrombotic and hemorrhagic complications in polycythemia vera can be life-threatening.

C. Diagnosis

1. Anemia with decreased reticulocyte count
2. Thrombocytopenia

3. Neutropenia
4. Peripheral blood smear—reveals normocytic anemia with Howell–Jolly bodies, basophilic stippling of RBCs, agranular platelets, or other evidence of dysplasia
5. Bone marrow biopsy—typically reveals dysplastic marrow cells with blasts or ringed sideroblasts
6. Cytogenetic studies often reveal chromosomal abnormalities or mutated oncogenes

Quick HIT

Clinical features in myelodysplastic syndromes are due to bone marrow failure and mimic those of aplastic anemia.

D. Treatment

1. Supportive treatment—mainstay of treatment
   a. RBC and platelet transfusions as necessary
   b. Erythropoietin—may help to reduce the number of blood transfusions necessary
   c. Granulocyte colony-stimulating factor—can be an effective adjunctive treatment for neutropenic patients
   d. Vitamin supplementation (particularly with vitamins B_6, B_{12}, and folate)—important given the increased turnover of marrow cells
2. Chemotherapy and immunosuppressive agents—may improve survival in some patients
3. Bone marrow transplantation

Essential Thrombocythemia

- Defined as platelet count >600,000/mm^3
- It is a disease with high morbidity but low mortality
- A diagnosis of exclusion—reactive thrombocytosis (due to infection, inflammation, bleeding) and other myeloproliferative disorders must be excluded
- It is primarily manifested by thrombosis (e.g., stroke, MI, DVT/PE), or paradoxically and less frequently, bleeding (due to defective platelet

function)

- Other findings may include vasomotor symptoms (headache, syncope, atypical chest pain, transient visual disturbances), splenomegaly, pseudohyperkalemia, elevated bleeding time, and erythromelalgia (burning pain and erythema of the extremities due to microvascular occlusions)
- Peripheral blood smear shows hypogranular, abnormally shaped platelets
- Bone marrow biopsy shows an increased number of megakaryocytes
- JAK2 tyrosine kinase mutation is seen up 60% to 65% of cases. Most other cases are driven by other mutations (MPL, CALR)
- Treatment usually involves antiplatelet agents (aspirin to reduce incidence of vascular events) and cytoreductive therapies with hydroxyurea or anagrelide

Infectious Diseases 10

Kelley Chuang

Infections of the Upper and Lower Respiratory Tracts

Pneumonia

A. General Characteristics

1. There are two types of pneumonia: community-acquired and nosocomial
   a. Community-acquired pneumonia (CAP)
      - Occurs in the community (infection acquired outside of the hospital)
      - Can be typical or atypical
      - **Most common bacterial pathogen is *Streptococcus pneumoniae***

   b. Nosocomial pneumonia (higher risk of multidrug resistance and nosocomial pathogens)
      - Two types: hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP)
      - HAP: pneumonia that develops ≥48 hours after hospital admission
      - VAP: pneumonia that develops ≥48 hours after endotracheal intubation
      - Healthcare-associated pneumonia (HCAP) was previously used to denote pneumonia that occurs in nursing homes or dialysis centers. This term is no longer used.
      - **Most common bacterial pathogens are gram-negative rods (*Escherichia coli, Pseudomonas, Klebsiella)* and *Staphylococcus aureus***

Quick HIT

- "Classic" CAP presents with fever, chills, pleuritic chest pain, dyspnea, and productive cough.
- The "atypical pneumonia" syndrome, associated with *Mycoplasma* or *Chlamydia* infection, often begins with URI symptoms (sore throat, rhinorrhea, headache), followed by a nonproductive cough and dyspnea.

2. There are three recommended methods of prevention
   a. Influenza vaccine—give yearly to people at increased risk for complications and to healthcare workers
   b. Pneumococcal vaccine—for patients >65 years and for younger people at high risk (e.g., those with heart disease, cochlear implants, sickle cell disease, pulmonary disease, diabetes, alcoholic cirrhosis, asplenia)
   c. SARS-CoV-2 vaccines—indicated for all patients and especially those with significant comorbidities or advanced age. See section on COVID-19 for details

Quick HIT

Most cases of CAP result from aspiration of oropharyngeal secretions because the majority of organisms that cause CAP are **normal inhabitants of the pharynx.**

B. Typical CAP

1. Common bacterial agents
   a. *S. pneumoniae* (60%)
   b. *Haemophilus influenzae* (15%)
   c. Aerobic gram-negative rods (6% to 10%)—*Klebsiella* (and other Enterobacteriaceae)
   d. *S. aureus* (2% to 10%)
2. Clinical features
   a. Symptoms
      - Acute onset of fever and shaking chills
      - Cough productive of thick, purulent sputum

- Pleuritic chest pain (suggests pleural effusion)
- Dyspnea

b. Signs
- Tachycardia, tachypnea
- Late inspiratory crackles, bronchial breath sounds, increased tactile and vocal fremitus, dullness on percussion
- Pleural friction rub (associated with pleural effusion)

3. Chest x-ray (CXR)
   a. Lobar consolidation
   b. Multilobar consolidation indicates very serious illness

Quick HIT

S. pneumoniae accounts for up to 66% of all cases of bacteremic pneumonia, followed by *H. influenzae*, influenza virus, and *Legionella* spp.

Quick HIT

Studies have shown that if vital signs are entirely normal, the probability of pneumonia in outpatients is less than 1%.

C. Atypical CAP

1. Common agents
   a. *Mycoplasma pneumoniae* (most common)
   b. *Chlamydia pneumoniae*
   c. *Chlamydia psittaci*
   d. *Coxiella burnetii* (Q fever)
   e. *Legionella* spp.
   f. Viruses: influenza virus (A and B), adenoviruses, parainfluenza virus, RSV, SARS-CoV-2 (COVID-19, discussed in detail later in this chapter)
2. Clinical features
   a. Symptoms
   - Insidious onset—headache, sore throat, fatigue, myalgias
   - Dry cough (no sputum production)

- Fevers (chills are uncommon)

b. Signs
  - Pulse-temperature dissociation—normal pulse in the setting of high fever is suggestive of atypical CAP
  - Wheezing, rhonchi, crackles

c. CXR
  - Diffuse reticulonodular infiltrates
  - Absent or minimal consolidation

Quick HIT

"Atypical" pneumonia refers to organisms not visible on Gram stain, not culturable on standard blood agar, and often intrinsically resistant to β-lactams.

Quick HIT

Sputum Culture CAP

- The value of routine sputum collection for Gram stain and culture is controversial. The Infectious Disease Society of America has advocated against obtaining routine sputum Gram stain and culture in adults with CAP managed in the outpatient setting. For hospitalized patients, sputum collection may be helpful for severe CAP or when concerned for multidrug-resistant organisms.
- A good sputum specimen has >25 PMNs and <10 epithelial cells per low-power field.

D. Diagnosis

1. PA and lateral CXR is the preferred method to confirm diagnosis (Figure 10-1) (see also Clinical Pearls 10-1 and 10-2).
   a. Considered sensitive—if CXR findings are not suggestive of pneumonia, do not treat the patient with antibiotics.
   b. After treatment, changes evident on CXR usually lag behind the clinical response (up to 6 weeks).
   c. Changes include interstitial infiltrates, lobar consolidation, and/or cavitation.

   d. False-negative chest radiographs occur with neutropenia, dehydration, infection with PCP (*Pneumocystis carinii* pneumonia), and early disease (<24 hours).
2. Chest CT is more sensitive for detecting pneumonia than CXR. Preferred for those with immunocompromised, to look for complications, and to rule out equivocal cases when pneumonia is clinically suspected but CXR is nondiagnostic.
3. Pretreatment expectorated sputum for Gram stain and culture—low sensitivity and specificity, but still worthwhile test if antimicrobial resistance is suspected.
   a. Sputum Gram stain—obtain if severe CAP.
      - Commonly contaminated with oral secretions.
      - A good specimen has a sensitivity of 60% and specificity of 85% for identifying gram-positive cocci in chains (*S. pneumoniae*).
   b. Sputum culture—try to obtain in all patients with severe CAP or those with suspected antimicrobial resistance.
      - Specificity is improved if the predominant organism growing on the culture media correlates with the Gram stain.
4. Special stains of the sputum in selected cases.
   a. Acid-fast stain (*Mycobacterium* spp.) if tuberculosis (TB) is suspected. If pulmonary TB is suspected, patient should be in airborne isolation while undergoing TB evaluation.
   b. Silver stain (fungi, *P. carinii*) for HIV/immunocompromised patients.
5. Urinary antigen assay for *Legionella* in selected patients.
   a. This test is very sensitive.
   b. The antigen persists in the urine for weeks (even after treatment has been started).
6. Consider two pretreatment blood cultures from different sites. Blood cultures positive in 5% to 15% of cases.

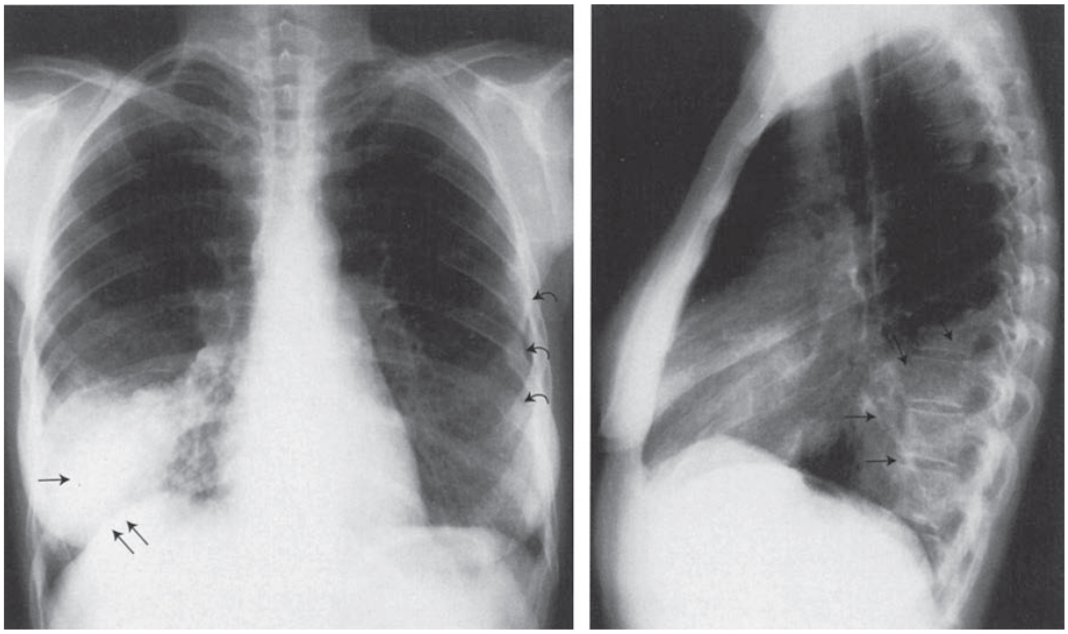
Quick HIT

Patients admitted to the hospital with suspected bacterial pneumonia should get:

- CXR (PA and lateral)
- Laboratory tests—CBC and differential, BMP
- O_2 saturation
- Two pretreatment blood cultures
- Gram stain and culture of sputum (if severe CAP or concern for antimicrobial resistance)
- Antibiotic therapy

Quick HIT

Radiographic changes and clinical findings do not help in identifying the causative pathogen in CAP.



A B

FIGURE
10-1 **Chest PA (A) and lateral (B) radiographs: Right lower lobe pneumonia (*straight arrows*). On the PA radiograph, the right cardiac border is clearly visible, and the right hemidiaphragm is partially silhouetted (*double straight arrows*). These findings indicate that the infiltrate is posterior or in the right lower lobe as confirmed on the lateral radiograph (*straight arrows*).**
(Reprinted with permission from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Lippincott-Raven; 1998:110. Figure 6–54A and B.)

CLINICAL PEARL 10-1

General Approach to Diagnosis of CAP

The first task is to **differentiate lower respiratory tract infection from the other causes of cough and from upper respiratory infection.**

- If nasal discharge, sore throat, or ear pain predominates, upper respiratory infection is likely.
- Once lower tract infection is suspected, the next task is to differentiate between pneumonia and acute bronchitis. Unfortunately, clinical features (cough, sputum, fever, dyspnea) are not reliable in differentiating between the two.
- CXR is the only reasonable method of differentiating between pneumonia and acute bronchitis.

CLINICAL PEARL 10-2

Pneumonia Pearls

- In those with alcohol use disorder, think of *Klebsiella pneumoniae;* in those with history of travel to or from developing countries, think of TB.
- In nursing home residents, consider a nosocomial pathogen and predilection for the upper lobes (e.g., *Pseudomonas*).
- HIV-positive patients are at risk for *P. carinii* and *M. tuberculosis,* but are still more likely to have a typical infectious agent.
- *Legionella* pneumonia is common in organ transplant recipients, patients with renal failure, patients with chronic lung disease, and smokers and presents with GI symptoms and hyponatremia. *Legionella* pneumonia is rare in healthy children and young adults.

Quick HIT

Test for microbial diagnosis for outpatients is not required. Empiric treatment is often successful if CAP is suspected.

Quick HIT

If patient is hypoxic or hypotensive, admit to hospital.

E. Treatment of CAP

1. Decision to hospitalize
   a. **The decision to hospitalize or treat as an outpatient is one of the most important decisions and is based on severity of disease.**
   b. One common clinical tool is the Pneumonia Severity index (PSI). Patients are stratified into five classes based on severity. The PSI can serve as a general guideline, but clinical judgment is critical in making this decision. The decision to admit the patient is not based on a specific organism (one does not have this information when making this decision).
2. Antimicrobial therapy

a. Because the specific cause is usually not determined on initial evaluation, empiric therapy is often required.

b. For outpatients
   - For healthy adults without comorbidities or risk factors for antibiotic resistance, the most common organisms are *S. pneumoniae, Mycoplasma, Chlamydia,* and *Legionella.* Treat with amoxicillin, doxycycline, or a macrolide antibiotic (azithromycin).
   - For older adults and patients with comorbidities (heart, liver, kidney, or lung disease, diabetes mellitus, alcohol use disorder, malignancy, or asplenia), or those who received antibiotics in the last 3 months, treat with combination therapy. Most commonly, amoxicillin/clavulanate PLUS azithromycin or doxycycline. Or a cephalosporin (cefpodoxime) PLUS azithromycin or doxycycline. Monotherapy is an option with a respiratory fluoroquinolone (levofloxacin), but less optimal due to adverse effects of fluoroquinolones.
   - For outpatients, treatment is continued for 5 days. Generally treat until patient has been afebrile for 48 hours.

c. For hospitalized patients, a third-generation cephalosporin PLUS a macrolide (i.e., ceftriaxone plus azithromycin), or a respiratory fluoroquinolone alone is appropriate.

Quick HIT

For uncomplicated CAP in patients without significant comorbidities, treat with a β-lactam such as amoxicillin or amoxicillin/clavulanate. Add a macrolide (azithromycin) or doxycycline for atypical coverage.

Quick HIT

For outpatients, treatment is continued for 5 days. Do not stop treatment until patient has been afebrile for 48 hours.

A 23-year-old man with a history of cystic fibrosis presents to the emergency department in respiratory failure. He is found to be febrile with leukocytosis and infiltrates on chest x-ray. Sputum Gram stain shows gram-negative rods, and culture grows oxidase-positive colonies that produce a sweet smell. Other significant laboratory values include a leukocyte count of 17,300/mm^3 and a creatinine of 1.6 mg/dL (baseline 0.9 mg/dL).

Which of the following is the most appropriate antibiotic for this patient?

A. Gentamicin
B. Cefepime
C. Vancomycin
D. Cephalexin

- **The answer is B: Cefepime.** *Pseudomonas* is a common respiratory infection in cystic fibrosis patients and is a major cause of mortality. It is a common nosocomial pathogen, seen in many cases of HAP and VAP, and is often MDR. It is also a common infectious agent in any immunocompromised patient, especially in burn and neutropenic patients. **(C)** MRSA is a gram-positive organism, and is not the most appropriate answer. **(A)** Aminoglycosides are not the *best* agent for this patient for two reasons: First, aminoglycosides are not the preferred drugs to treat pneumonia; second, the patient is suffering from acute kidney injury and aminoglycosides have a high rate of nephrotoxicity. **(D)** Cephalexin has no activity against *Pseudomonas.*

F. Treatment of Hospital-Acquired Pneumonia

1. **Treatment is tailored toward gram-negative rods, specifically with antibiotics with antipseudomonal activity (any of the following are appropriate):**
   a. Cephalosporins with pseudomonal coverage: ceftazidime or cefepime

b. Carbapenems: imipenem or meropenem
c. Penicillins: piperacillin/tazobactam
d. Fluoroquinolones: ciprofloxacin, levofloxacin
e. Aminoglycosides: amikacin, gentamicin (usually reserved for critically ill due to high amount of adverse effects)
f. Polymyxins: colistin (as with aminoglycosides, usually reserved)

2. **Macrolides are not used as single-agent therapy**

> ***Quick* HIT**
>
> Pleural effusion is common in patients with pneumonia. Progression to empyema (infected, loculated pleural fluid) requires chest tube drainage.

G. Complications

1. Pleural effusion ("parapneumonic effusions")—see Chapter 2.
   a. Can be seen in more than 50% of patients with CAP on routine CXR. Empyema is infrequent in these patients.
   b. Most of these effusions have an uncomplicated course and resolve with treatment of the pneumonia with antibiotics.
   c. Thoracentesis should be performed if the effusion is significant (>1 cm on lateral decubitus film) or patient does not respond as expected to empiric antibiotics. Send fluid for Gram stain, culture, pH, cell count, determination of glucose, protein, and LDH levels.
2. Pleural empyema occurs in 1% to 2% of all cases of CAP (up to 7% of hospitalized patients with CAP). See Chapter 2.
3. Acute respiratory failure may occur if the pneumonia is severe.

> ***Quick* HIT**
>
> **Lung Abscess Pearls**
>
> - The dependent zones of the lungs are most likely to be infected by aspirated contents—the posterior segments of the upper lobes and posterior segments of the lower lobes.
> - Aspirated material is more likely to affect the right lung because the right mainstem bronchus is wider, straighter, and shorter.

Ventilator-Associated Pneumonia

A. Patients on mechanical ventilation are at risk of developing pneumonia because the normal mucociliary clearance of the respiratory tract is impaired (cannot cough). Also, positive pressure impairs the ability to clear colonization.

B. Findings to help with diagnosis: new infiltrate on CXR, purulent secretions from endotracheal tube, fever, worsening hypoxemia, rising WBC count.

C. Bronchoalveolar lavage (BAL)—bronchoscope passed into lungs to get cultures.

D. Treatment is with a combination of antibiotics with anti-MRSA activity (if at risk for MRSA) such as vancomycin OR linezolid, with one or more of the following drugs with antipseudomonal activity:

1. Cephalosporin with antipseudomonal activity (ceftazidime or cefepime)
2. β-Lactam and β-lactamase inhibitor (piperacillin/tazobactam)
3. Carbapenem (imipenem or meropenem)
4. An additional antibiotic may be added for “double GNR coverage” if high risk for multidrug-resistant VAP: aminoglycoside OR fluoroquinolone

Lung Abscess

A. General Characteristics

1. Abscess in the lung parenchyma results when infected lung tissue becomes necrotic and forms suppurative cavitary lesions. The typical case is aspiration of a large volume of oropharyngeal contents or food, with resulting pneumonia and necrosis when adequate treatment is not administered. Most patients who have aspiration pneumonia are treated promptly, thereby avoiding abscess formation

2. By definition, a lung abscess is formed by one or more cavities, with a circumscribed area of pus caused by infection
3. Lung abscesses can be complications of the following:
   a. Aspiration of organisms
   b. Acute necrotizing pneumonia (gram-negative rods)
   c. Hematogenous spread of infection from distant site
   d. Direct inoculation with contiguous spread
4. Causative organisms are mainly bacteria that colonize the oropharynx
   a. Oral anaerobes: *Prevotella, Peptostreptococcus, Fusobacterium, Bacteroides* spp.
   b. Other bacteria: *S. aureus, S. pneumoniae,* and aerobic gram-negative bacilli
5. Epidemiology/risk factors
   a. The main risk factor is predisposition to aspiration. This may be seen in patients with impaired consciousness (alcohol use disorder, seizures), dysphagia, neurologic conditions (CVA), or mechanical disruption of normal defense mechanisms (nasogastric or endotracheal tube)
   b. Poor dental hygiene increases the content of oral anaerobes

B. Clinical Features

1. The majority of cases have an indolent onset; some present more acutely.
2. Common symptoms and signs
   a. Cough—Foul-smelling sputum is consistent with anaerobic infection. It is sometimes blood tinged
   b. Shortness of breath
   c. Fever, chills
   d. Constitutional symptoms: fatigue, malaise, weight loss

C. Diagnosis

1. CXR
   a. This reveals thick-walled cavitation with air–fluid levels
   b. Look for abscess in dependent, poorly ventilated lobes
2. CT scan is test of choice as it provides more information about anatomic location of abscess than CXR and can identify other

associated findings (e.g., malignancy, lymphadenopathy)
3. Sputum Gram stain and culture has low sensitivity and specificity
4. Consider obtaining cultures via bronchoscopy or transtracheal aspiration rather than simple expectoration to avoid contamination with oral flora

D. Treatment

1. Hospitalization is often required if lung abscess is found. Drainage of abscess (percutaneous or transbronchoscopic) may be needed if no or minimal response to antibiotics after 7 days
2. Antimicrobial therapy
   a. Antibiotic regimens include coverage for the following:
      - Gram-positive cocci—ampicillin/sulbactam or amoxicillin/clavulanic acid, ampicillin/sulbactam, or vancomycin for *S. aureus*
      - Anaerobes—clindamycin or metronidazole
      - If gram-negative organisms are suspected, add a fluoroquinolone, cefepime, ceftazidime, or a carbapenem

   b. Continue antibiotics until the cavity is gone or until imaging findings have improved considerably—this may take months!

***Quick* HIT**

TB is a leading cause of death due to infection worldwide.

Tuberculosis

A. General Characteristics

1. Microbiology
   a. Caused by *Mycobacterium tuberculosis*
   b. Mycobacteria are acid-fast bacilli (AFB)—considered slow growing but hardy organisms
   c. Inhibited by the cellular arm of the immune system
2. Transmission

a. Transmission occurs via inhalation of aerosolized droplets containing the active organism
b. Only those people with active pulmonary or laryngeal TB are contagious (e.g., by coughing, sneezing)
c. People with latent TB or isolated extrapulmonary TB are not contagious

3. Pathophysiology
   a. Primary TB
      - Bacilli are inhaled and deposited into the lung, then ingested by alveolar macrophages
      - Surviving organisms multiply and disseminate via lymphatics and the bloodstream. Granulomas form and "wall off" the mycobacteria. The granulomas in oxygen-rich areas, such as the lungs, allow these organisms to remain viable (they are aerobes). After the resolution of the primary infection, the organism remains dormant within the granuloma
      - An insult to the immune system may activate the TB at any time
      - Only 5% to 10% of individuals with primary TB will develop active disease in their lifetime
   b. Secondary TB (reactivation)
      - Occurs when the host's immunity is weakened (e.g., HIV infection, malignancy, immunosuppressants, substance abuse, poor nutrition)
      - Usually manifests in the most oxygenated portions of the lungs—the apical/posterior segments
      - Produces clinical manifestations of TB
      - Can be complicated by hematogenous or lymphatic spread, resulting in miliary TB
   c. Extrapulmonary TB
      - Individuals with impaired immunity may not be able to contain the bacteria at either the primary or the secondary stage of the infection
      - This may result in active disease throughout the body
      - It is common in patients with HIV because cellular immunity is impaired

4. Risk factors (almost all patients with TB have one or more of the following):
   a. HIV infection
   b. Birth in or immigration from a TB-endemic area within last 5 years
   c. Incarceration
   d. Healthcare workers
   e. Close contacts of someone with TB
   f. Substance use disorder
   g. Diabetes mellitus
   h. Glucocorticoid/immunosuppressant medications
   i. Solid organ or hematopoietic transplant
   j. Hematologic malignancy
   k. Malnutrition
   l. Low socioeconomic status

Quick HIT

Radiographic Findings in Primary TB

- Ghon complex—calcified primary focus with an associated lymph node
- Ranke complex—when Ghon complex undergoes fibrosis and calcification

B. Clinical Features

1. Primary TB
   a. **Usually asymptomatic**
   b. Hilar lymphadenopathy and pleural effusion may develop
   c. If the immune response is incomplete, the pulmonary and constitutional symptoms of TB may develop. This is known as progressive primary TB
2. Secondary (active) TB, also known as reactivation TB
   a. Constitutional symptoms—fever, night sweats, weight loss, and malaise are common
   b. Cough progresses from dry cough to purulent sputum. Hemoptysis suggests advanced TB
   c. Apical rales may be present on examination
3. Extrapulmonary TB

a. May involve any organ. The lymph nodes, pleura, genitourinary tract, spine, intestine, and meninges are some of the common sites of infection
b. Miliary TB refers to hematogenous dissemination of the tubercle bacilli
   - May be due to a reactivation of dormant, disseminated foci or a new infection
   - Also common in patients with HIV
   - May present with organomegaly, reticulonodular infiltrates on CXR or CT chest (Figure 10-2), and choroidal tubercles in the eye

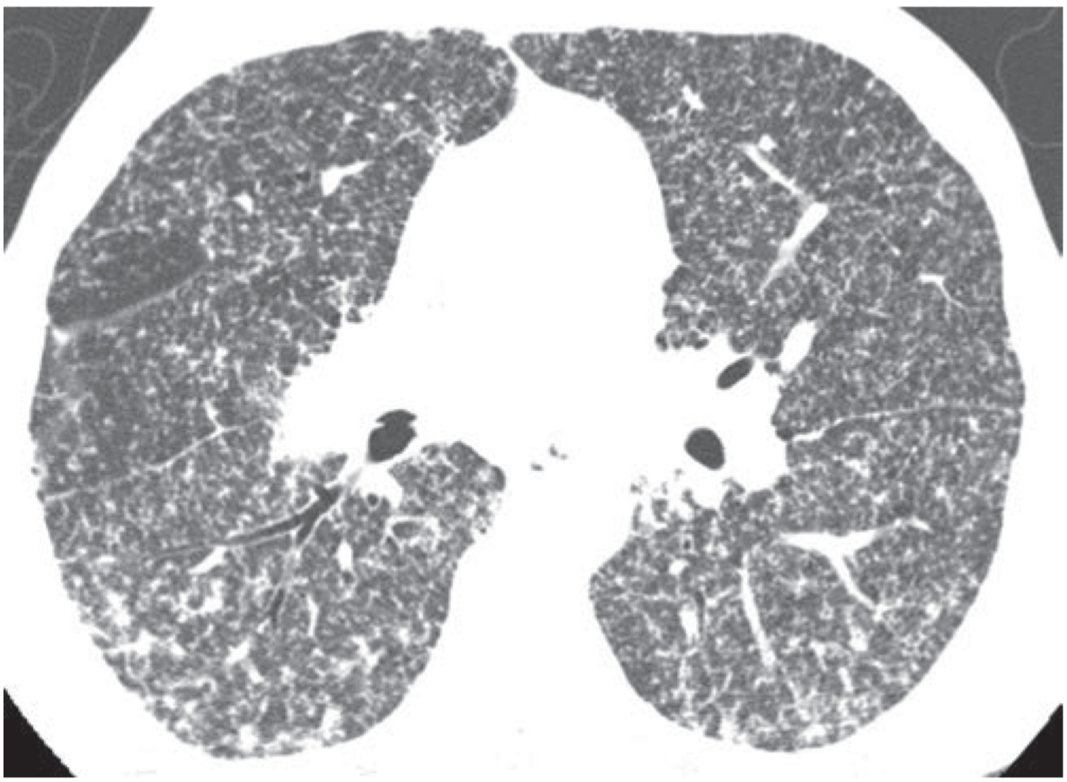


FIGURE 10-2 **Cross-sectional CT chest with miliary tuberculosis. Diffuse, small, evenly distributed nodules are present.** (Reprinted with permission from Elicker BM, Webb WR. *Fundamentals of High-Resolution Lung CT: Common Findings, Common Patterns, Common Diseases, and Differential Diagnosis*. Wolters Kluwer Health/Lippincott Williams & Wilkins, 2013. Figure 14.13.)

Quick HIT

Diagnosis of TB is challenging in patients with HIV because:

- PPD skin test result is negative.
- Patients have "atypical" CXR findings.
- Sputum smears are more likely to be negative.
- Granuloma formation may not be present in the late stages.

C. Diagnosis

a. Must have a high index of suspicion, depending on patient's risk factors and presentation

b. CXR

   a. Classic findings are **upper lobe infiltrates with cavitations**

   b. Other possible findings

      - Pleural effusion(s)
      - *Ghon complex* and *Ranke complex:* evidence of healed primary TB
      - Atypical findings common in immunocompromised patients

c. Sputum studies (sputum acid-fast bacilli or AFB testing)

   a. Definitive diagnosis is made by sputum culture—growth of *M. tuberculosis*

   b. Obtain three sputum specimens 8 hours apart (at least one should be collected in early morning)—culture takes 4 to 8 weeks

   c. PCR can detect specific mycobacterial DNA more rapidly

   d. Diagnosis is sometimes made by finding AFB on microscopic examination, but this is not definitive because other mycobacteria may colonize airways

d. Tuberculin skin test (PPD test) and interferon-gamma release assay (IGRA)

   a. Both PPD and IGRA are screening tests to detect those who may have been exposed to TB. They are not for diagnosis of active TB, but rather of latent (primary) TB (a positive CXR is used to diagnose active TB). If patient is symptomatic or has abnormal CXR, order a sputum acid-fast test, not a PPD

   b. Inject PPD into the volar aspect of forearm. Measure the amount of induration 48 to 72 hours later. Positive result is interpreted as follows:

- Patients with no risk factors: induration ≥15 mm
- Certain high-risk populations e.g., those who live or were born in high-prevalence areas, patients who live in high-risk congregate settings (e.g., hospitals, nursing homes, homeless shelters, or correctional facilities), patients with substance use disorder, and certain medical conditions (e.g., diabetes, advanced CKD): induration >10 mm
- Patients with HIV, organ transplant recipients, close contacts of those with ACTIVE TB, patients with immunosuppression (e.g., prolonged corticosteroids), or those with radiographic evidence of primary TB: induration ≥5 mm
- If initial PPD is negative in a close contact of someone with active TB, a repeat test should be done in 8 to 10 weeks after last exposure as reaction may be delayed

c. Many persons born outside of the United States have received the Bacille Calmette–Guerin (BCG) vaccine, which may cause a positive PPD skin test. These patients should instead receive the IGRA test to screen for latent TB

d. IGRA is a blood test that measures an immune response to *M. tuberculosis*. Can be done in one visit (does not require two visits like PPD). If positive, suggests *M. tuberculosis* infection. If negative, suggests against infection (but cannot be used to rule out active TB). May result as indeterminate in those with immunocompromise

e. If PPD or IGRA is positive in a patient without symptoms, a CXR is needed to rule out active disease. Once active disease is excluded, treatment of latent TB is initiated. A patient with a positive PPD test has a 10% lifetime risk of TB, and this risk is reduced to 1% after treatment

Quick HIT

Patients previously vaccinated with BCG will have a false-positive PPD test. They should instead receive a TB blood test such as an interferon-gamma release assay (IGRA).

Quick HIT

INH should always be started with vitamin B_6 (pyridoxine) to prevent symptoms of B_6 deficiency, which include stomatitis, glossitis, cheilosis, convulsions, hyperirritability, peripheral neuropathy, and sideroblastic anemia.

D. Treatment

1. Patients with active TB must be isolated until sputum is negative for AFB.
   a. First-line therapy is a four-drug regimen: rifampin, isoniazid (INH), pyrazinamide, and ethambutol. This regimen is also known as RIPE therapy.
   b. The initial treatment regimen consists of 2 months of treatment with the four-drug regimen. The initial 2-month phase is followed by a 4-month phase of INH and rifampin. There are other variations, including a shortened 4-month regimen with INH, rifapentine, moxifloxacin, and pyrazinamide.
2. Treatment of latent (primary) TB (i.e., positive PPD skin test or IGRA) should be started **after** active TB has been excluded (negative CXR, sputum, or both). There are several options for treatment, including rifampin for 4 months, isoniazide PLUS rifampin or rifapentine for 3 months, or isoniazide monotherapy for 9 months.

Quick HIT

- For a positive TB exposure and a positive PPD test (but no active disease), treatment options include rifampin only, INH only, or INH plus rifampin or rifapentine.
- If the patient has active TB, multiagent therapy is indicated.

Quick HIT

All TB medications can cause hepatotoxicity. Discontinue treatment only if liver transaminases rise to three to five times the upper limit of normal.

Influenza

- An orthomyxovirus transmitted via respiratory droplets, typically occurring in winter months.
- Antigenic types A and B are responsible for the clinical syndrome known as the “flu.”
- Annual epidemics are due to minor genetic reassortment and usually are not life-threatening except in the very young, the very old, the immunocompromised, and hosts with significant medical comorbidities.
- Influenza pandemics are due to major genetic recombination and are often fatal, even in young, otherwise healthy hosts.
- Clinical findings are a rapid onset of fever, chills, malaise, headache, nonproductive cough, and sore throat. Nausea may also be present.
- Treatment is largely supportive. Antiviral agents are available but these are only indicated in patients with severe disease (requiring hospitalization) or at high risk of complications and must be given within the first 48 hours of illness. Give antibiotics only for secondary bacterial infections. (See Chapter 12 for vaccination recommendations.)
- A neuraminidase inhibitor (zanamivir or oseltamivir) is the recommended antiviral agent.

SARS-CoV-2 (COVID-19)

A. General Characteristics

1. SARS-CoV-2 or COVID-19 is a novel coronavirus identified in 2019. It has since rapidly spread into a global pandemic.
2. Understanding of this disease is evolving, and new variants of concern continue to emerge.
3. The virus is spread primarily through person-to-person respiratory transmission. It is thought to occur through close-range contact with respiratory particles.

B. Clinical Features

1. Can be asymptomatic
2. Symptoms range from mild-to-severe disease with respiratory failure

    a. Risk factors for severe illness include advanced age, underlying medical conditions (e.g., cancer, CKD, diabetes mellitus, among others), and low socioeconomic status.
3. Known symptoms include cough, myalgias, headache, and dyspnea
4. Other common symptoms: diarrhea, sore throat, loss of taste or smell
5. Complications:
    a. Acutehypoxic respiratory failure (sometimes in absence of dyspnea)
    b. Thromboembolic complications can occur
    c. Patients are at increased risk of stroke and other neurologic complications
    d. Other sequelae have yet to be fully characterized

C. Diagnosis

1. Diagnosis is confirmed by SARS-CoV-2 PCR or antigen testing. Nasopharyngeal swab is the most reliable method of collection
2. Common lab abnormalities:
    a. Lymphopenia, thrombocytopenia
    b. Elevated AST and ALT
    c. Elevated inflammatory markers (ESR, CRP)
    d. Elevated D-dimer
3. Chest x-ray or chest CT often shows diffuse bilateral ground-glass opacities

D. Treatment

1. Treatment consists largely of supportive care (supplemental oxygen).
2. Other treatments such as corticosteroids, antiviral therapy (e.g., remdesivir), and monoclonal antibodies can be used in selected populations and are actively being studied.
3. Key strategy is prevention with SARS-CoV-2 vaccination. There are multiple vaccine formulations including mRNA vaccines and others in development. This is an evolving field.

Infections of the Central Nervous System

Meningitis

A. General Characteristics

1. This refers to inflammation of the meningeal membranes that envelop the brain and spinal cord. It is usually associated with infectious causes, but noninfectious causes (such as medications, SLE, sarcoidosis, and carcinomatosis) also exist
2. Pathophysiology
   a. Infectious agents frequently colonize the nasopharynx and respiratory tract
   b. These pathogens typically enter the CNS via one of the following:
      - Invasion of the bloodstream, which leads to hematogenous seeding of CNS
      - Retrograde transport along cranial (e.g., olfactory) or peripheral nerves
      - Contiguous spread from sinusitis, otitis media, surgery, or trauma
3. Can be classified as acute or chronic, depending on onset of symptoms
   a. Acute meningitis—onset within hours to days. Bacterial meningitis often presents this way
   b. Chronic meningitis—onset within weeks to months; commonly caused by viruses, mycobacteria, fungi, spirochetes, or parasites
4. Another important distinction is bacterial versus aseptic (described below)

Quick HIT

Acute bacterial meningitis is a medical emergency requiring prompt recognition and antibiotic therapy. It is frequently fatal, even with appropriate treatment.

5. Acute bacterial meningitis
   a. Causes

- Neonates—Group B streptococci, *E. coli, Listeria monocytogenes*
- Children >3 months—*Neisseria meningitidis, S. pneumoniae, H. influenzae*
- Adults (ages 18 to 50 years)—*S. pneumoniae, N. meningitidis, H. influenzae*
- Elderly (>50 years)—*S. pneumoniae, N. meningitidis, L. monocytogenes,* gram-negative bacilli
- Immunocompromised—*L. monocytogenes,* gram-negative bacilli, *S. pneumoniae*
- *S. aureus* and other staphylococci can cause bacterial meningitis in all ages, especially in those with recent surgery, indwelling devices, or skin infections

b. Complications

- Seizures, coma, brain abscess, subdural empyema, DIC, respiratory arrest
- Permanent sequelae—deafness, brain damage, hydrocephalus

Quick HIT

Acute Bacterial Meningitis (clinical features)

Characteristic triad includes (but may not be present in all patients):

- Fever
- Nuchal rigidity
- Change in mental status

6. Aseptic meningitis

a. The term aseptic meningitis refers to meningeal inflammation with negative bacterial cultures.

b. Aseptic meningitis is most commonly caused by a variety of nonbacterial pathogens, frequently viruses such as enterovirus and herpes simplex virus (HSV). It can also be caused by certain bacteria, parasites, and fungi. Certain medications, malignancies, and autoimmune disorders can also cause aseptic meningitis.

c. **It may be difficult to distinguish it clinically from acute bacterial meningitis.** If there is uncertainty in diagnosis, treat for acute bacterial meningitis.

d. It is associated with a better prognosis than acute bacterial meningitis.

B. Clinical Features

1. Symptoms (any of the following may be present)
   a. Headache (may be more severe when lying down)
   b. Fevers
   c. Nausea and vomiting
   d. Stiff, painful neck
   e. Malaise
   f. Photophobia
   g. Alteration in mental status (confusion, lethargy, even coma)
2. Signs (any of the following may be present)
   a. Nuchal rigidity: stiff neck, with resistance to flexion of spine (may be absent)
   b. Rashes
      - Maculopapular rash with petechiae—purpura is classic for *N. meningitidis*
      - Vesicular lesions in varicella or HSV
   c. Increased ICP and its manifestations—for example, papilledema, seizures
   d. Cranial nerve palsies
   e. *Kernig sign*—inability to fully extend knees when patient is supine with hips flexed (90 degrees). Caused by irritation of the meninges (Figure 10-3)
   f. *Brudzinski sign*—flexion of legs and thighs that is brought on by passive flexion of neck for same reason as above. Both Kernig and Brudzinski signs have very poor sensitivity
   g. *Jolt test*—worsening headache when patient is asked to turn head back and forth quickly at frequency of at least 3 turns per second. Most sensitive and specific for acute bacterial meningitis

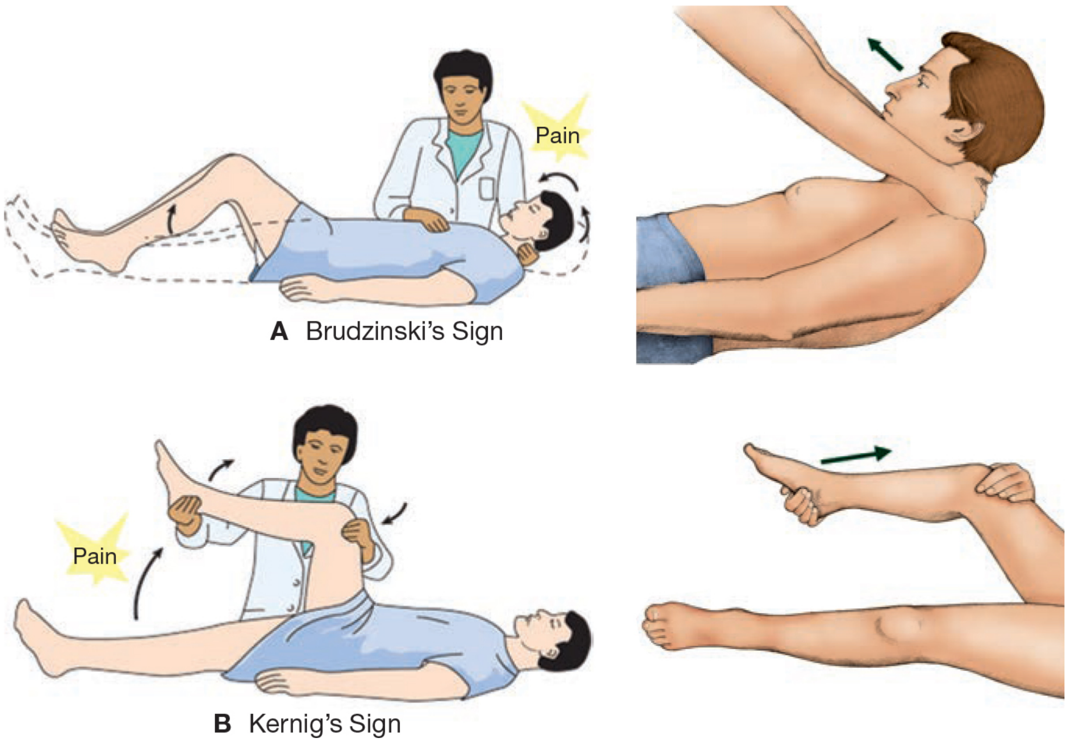


FIGURE 10-3 **Brudzinski sign and Kernig sign.**
(Reprinted with permission from Nettina SM. *Lippincott Manual of Nursing Practice*. 10th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013. Figure 15-5.)

TABLE 10-1 CSF Findings in Bacterial Versus Aseptic Meningitis

	Normal	Bacterial Meningitis	Aseptic Meningitis
WBC count (cells/mm^3)	<5	>1,000 (1,000–20,000)	<1,000
WBC differential	All lymphocytes or monocytes; no PMNs	Mostly PMNs	Mostly lymphocytes and monocytes
Glucose (mg/dL)	50–75	Low	Normal or low
Protein (mg/dL)	<60	High	Moderate elevation

C. Diagnosis

1. CSF examination (LP)—Perform this if meningitis is a possible diagnosis unless there is evidence of increased ICP or severe bleeding

diathesis (see Table 10-1). Also note the opening pressure

a. Examine the CSF. Cloudy CSF is consistent with a pyogenic leukocytosis
b. CSF should be sent for the following: cell count and differential, glucose, protein, Gram stain, and bacterial culture (including AFB), and other tests depending on clinical suspicion (cryptococcal antigen, other infectious immunoassays, PCR testing, etc.)
c. Bacterial meningitis—pyogenic inflammatory response in CSF
   - Elevated WBC count—PMNs predominate
   - Low glucose
   - High protein
   - Gram stain—positive in 75% to 80% of patients with bacterial meningitis
d. Aseptic meningitis—nonpyogenic inflammatory response in CSF.
   - There is an increase in mononuclear cells. Typically a lymphocytic pleocytosis is present
   - Protein is normal or slightly elevated
   - Glucose is usually normal. Some infections (such as TB and fungal meningitis) are associated with low glucose
   - CSF may be completely normal

2. CT scan of the head is recommended before performing an LP if there are focal neurologic signs, history of CNS disease, recent seizure, abnormal mentation, papilledema, or the patient is immunocompromised. If unable to obtain timely CT in the above patients and bacterial meningitis is suspected, proceed to empiric treatment (high mortality if bacterial meningitis is untreated)
3. Obtain blood cultures before antibiotics are given

A 54-year-old woman with a history of rheumatoid arthritis and hypertension presents to the emergency department with a high fever and headache. The symptoms began last night and were worse this morning. She also complains of severe sensitivity to light. Her medications include hydrochlorothiazide and methotrexate. She denies any cough, weight loss, chest pain, shortness of breath, or abdominal pain, and she has no history of chronic headaches or neurologic disease. Her temperature is 39.5°C, blood pressure is 146/90 mmHg, heart rate is 88 beats per minute, and respiratory rate is 14 breaths per minute. She is somewhat confused, there is significant nuchal rigidity, and her headache becomes worse when she moves her head quickly to the side. The neurologic examination, including a cranial nerve examination, is unremarkable. A funduscopic examination shows bilateral blurring of the optic disk margins and retinal venous engorgement.

Which of the following should be performed next in the workup of this patient?

A. CT scan
B. MRI
C. Lumbar puncture
D. Empiric azithromycin

- **The answer is A: CT scan.** The suspected diagnosis here is meningitis, and a CT scan should be performed first to rule out mass effect before a lumbar puncture is performed. CT scan should be performed in patients thought to be at high risk for cerebral herniation. Risk factors include papilledema, previous CNS disease, a seizure in the past week, immunosuppression, altered mental status, and focal neurologic signs. **(C)** This patient has both papilledema and immunosuppression (methotrexate), and therefore, a CT scan should be performed before a lumbar puncture to assess the risk for cerebral herniation during lumbar puncture. **(B)** An MRI

provides better visualization of the brain; however, it is costly and time-consuming. Because the purpose here is to rule out mass effect, a CT scan can do this adequately and quickly. **(D)** It is appropriate to administer empiric antibiotics early (and in cases for which there is high suspicion for bacterial meningitis, empiric antibiotics should be administered prior to CT or LP to avoid delay in treatment), but azithromycin is not an appropriate empiric antibiotic for meningitis.

D. Treatment

1. Bacterial meningitis.
   a. Empiric antibiotic therapy—Start immediately after LP is performed. If a CT scan must be performed or if there are anticipated delays in LP, give antibiotics first. Pathogen can often still be identified from CSF several hours after administration of antibiotics. Delay in antibiotics leads to higher mortality
   b. Intravenous (IV) antibiotics
      - Initiate immediately if the CSF is cloudy or if bacterial infection is suspected.
      - Begin empiric therapy according to the patient's age (see Table 10-2)
      - Modify treatment as appropriate based on Gram stain, culture, and sensitivity findings
   c. Steroids—give IV glucocorticoids (dexamethasone) before or with antibiotics to prevent neurologic complications. Continue if CSF or blood cultures reveal *S. pneumoniae*
   d. Vaccination
      - Vaccinate all adults ≥65 years for *S. pneumoniae*
      - Vaccinate asplenic patients for *S. pneumoniae, N. meningitidis,* and *H. influenzae* (encapsulated organisms)
      - Vaccinate adolescents and immunocompromised patients for *N. meningitidis*.
   e. Prophylaxis (e.g., rifampin, ciprofloxacin, or ceftriaxone)—for all close contacts of patients with meningococcus
2. Aseptic meningitis

a. Therapy is targeted at underlying cause. If viral, no specific therapy other than supportive care is required. The disease is usually self-limited. If fungal, parasitic, or TB, treat causative organism
b. Analgesics and fever reduction may be appropriate

TABLE 10-2 Empiric Treatment for Acute Bacterial Meningitis

Age or Risk Factor	Likely Etiology	Empiric Treatment
Infants (<3 mo)	Group B streptococci, *E. coli, Klebsiella* spp., *L. monocytogenes*	Cefotaxime + ampicillin + vancomycin (or ampicillin + aminoglycoside if <4 wk)
3 mo–50 yrs	*N. meningitidis, S. pneumoniae, H. influenzae*	Ceftriaxone or cefotaxime + vancomycin
>50 yrs	*S. pneumoniae, N. meningitidis, L. monocytogenes*, Gram-negative bacilli	Ceftriaxone or cefotaxime + vancomycin + ampicillin
Impaired cellular immunity (e.g., HIV)	*S. pneumoniae, N. meningitidis, L. monocytogenes,* aerobic gram-negative bacilli (including *P. aeruginosa*)	Cefepime + ampicillin + vancomycin (or meropenem + vancomycin)

Encephalitis

A. General Characteristics

1. Encephalitis is a diffuse inflammation of the brain parenchyma and is often seen simultaneously with meningitis. Meningitis (inflammation of the meninges) does not cause abnormalities in cerebral function. Encephalitis (inflammation of the brain) often causes alterations in behavior, personality, speech, sensation, or movement. There may be overlap
2. It is usually viral in origin. Nonviral causes, however, must also be considered
   a. Viral causes
      - Herpes (HSV-1)

- Arbovirus—for example, Eastern equine encephalitis, West Nile virus
- Enterovirus—for example, polio
- Less common causes—for example, measles, mumps, EBV, CMV, VZV, rabies, and prion diseases such as Creutzfeldt–Jakob disease

b. Nonviral infectious causes
- Toxoplasmosis
- Cerebral aspergillosis

c. Noninfectious causes
- Autoimmune
- Paraneoplastic

Quick HIT

Differential diagnosis in patients with fever and altered mental status: infection
- Sepsis, UTI, pneumonia, bacterial or aseptic meningitis, intracranial abscess, subdural empyema, medication/drugs
- Neuroleptic malignant syndrome (haloperidol, phenothiazines)
- Delirium tremens, metabolic derangements
- Thyroid storm

3. Risk factors
   a. AIDS—patients with AIDS are especially at risk for toxoplasmosis when the CD4 count is <200
   b. Other forms of immunosuppression
   c. Travel in underdeveloped countries
   d. Exposure to insect (e.g., mosquito) vector in endemic areas
   e. Exposure to certain wild animals (e.g., bats) in an endemic area for rabies
4. The overall mortality associated with viral encephalitis is approximately 10%

B. Clinical Features

1. Patients often have a nonspecific prodrome of fever, headache, malaise, and myalgias.

2. Within hours to days, patients become more acutely ill and progress to signs and symptoms of meningitis (e.g., photophobia, nuchal rigidity).
3. In addition, patients have altered sensorium, possibly including confusion, delirium, disorientation, and behavior abnormalities.
4. Focal neurologic findings (e.g., hemiparesis, aphasia, cranial nerve lesions) and seizures may also be present.

C. Diagnosis

1. Routine laboratory tests (to rule out nonviral causes) include CXR, urine and blood cultures, urine toxicology screen, and serum chemistries.
2. Perform an LP to examine CSF, unless the patient has signs of significantly increased ICP or other indications for CT before LP.
   a. Lymphocytosis (>5 WBC/mL) with normal glucose is consistent with viral encephalitis (similar CSF as in viral meningitis). CSF cultures are usually negative. Red cells in a nontraumatic tap suggest HSV-1.
   b. **CSF PCR** is the most specific and sensitive test for diagnosing many various viral encephalitides, including HSV-1, CMV, EBV, and VZV.
   c. CSF serologies for HIV and arboviruses can be helpful depending on the exposure history.
3. MRI of the brain is the imaging study of choice.
   a. Can rule out focal neurologic causes, such as an abscess.
   b. Increased areas of T2 signal in the frontotemporal localization are consistent with HSV encephalitis.
4. EEG can be helpful in diagnosing HSV-1 encephalitis—it would show unilateral or bilateral temporal lobe discharges.
5. Brain biopsy is a last resort in an acutely ill patient with a focal, enhancing lesion on MRI without a clear diagnosis after extensive workup.

Quick HIT

Not all brain abscesses are bacterial—especially in immunocompromised hosts!

- *Toxoplasma gondii* and fungi in patients with HIV/AIDS
- *Candida* spp., *Aspergillus* spp., or zygomycosis in neutropenic patients

D. Treatment

1. Supportive care, mechanical ventilation if necessary
2. Antiviral therapy
   a. There is no specific antiviral therapy for most causes of viral encephalitis
   b. HSV encephalitis—acyclovir for 2 to 3 weeks
   c. CMV encephalitis—ganciclovir or foscarnet
3. Management of possible complications
   a. Seizures—require anticonvulsant therapy
   b. Cerebral edema—treatment may include hyperventilation, osmotic diuresis, and steroids

Infections of the Gastrointestinal Tract (see also Chapter 3)

Viral Hepatitis

A. General Characteristics

1. Hepatitis means inflammation of the liver. There are many noninfectious types of hepatitis, such as alcoholic hepatitis, drug-induced hepatitis, autoimmune hepatitis, and numerous hereditary diseases.
2. Causes of viral hepatitis.
   a. There are five well-understood, main categories of viral hepatitis: hepatitis A, B, C, D, and E. Hepatitis viruses are often abbreviated by their type (i.e., HAV is hepatitis A virus, HBV is hepatitis B virus, and so forth).
   b. Other viruses that can cause one form or another of hepatitis are EBV, CMV, and HSV. These are not commonly associated with hepatitis in immunocompetent patients.

Quick HIT

- **Hepatitis B** is associated with polyarteritis nodosoa (PAN).
- **Hepatitis C** is associated with cryoglobulinemia.

3. Transmission varies depending on the specific virus.
   a. Hepatitis A and E are transmitted via the fecal–oral route and are more prevalent in developing countries.
   b. Hepatitis E is particularly prevalent in resource-limited countries. The highest prevalence is in Asia, Africa, parts of Europe. Its prevalence in the United States is declining.
   c. **Hepatitis B is transmitted parenterally or sexually.** Perinatal or vertical transmission is also possible and is a significant health issue

in parts of Africa and Asia.

d. Hepatitis D requires the outer envelope of the hepatitis B surface antigen (HB_SAG) for replication and therefore can be transmitted only as a coinfection with HBV, or as a superinfection in a chronic HBV carrier.

e. **The main route of transmission for hepatitis C is parenteral,** and it is therefore more prevalent in those with injection drug use. Sexual or perinatal transmission is not common.

f. **Hepatitis B, C, and D are the types that can progress to chronic disease.**

Quick HIT

In general, HAV and HEV cause a milder form of hepatitis and do not become chronic.

B. Clinical Features

1. Classified as acute (<6 months of liver inflammation) or chronic (>6 months of persistent liver inflammation) (Figure 10-4)
2. Acute hepatitis has a wide spectrum of clinical presentations, ranging from virtually asymptomatic to fulminant liver failure
   a. General clinical features
      - Jaundice—look in the sclera and under the tongue, because these may be the first places jaundice can be detected, especially in those with darker skin pigmentation
      - Dark-colored urine may be present (due to conjugated hyperbilirubinemia)
      - RUQ pain
      - Nausea and vomiting
      - Fever and malaise
      - Hepatomegaly may also be present

   b. In severe cases, acute hepatitis may result in liver failure and its complications. This is known as fulminant hepatitis (uncommon) and may be life-threatening. It occurs more commonly in hepatitis B, D, and E than in other types. Complications include:
      - Hepatic encephalopathy—Look for **asterixis** and **ataxia**

- Hepatorenal syndrome
- Bleeding diathesis—this occurs only when liver function is very compromised

c. Sometimes acute hepatitis may only present with transient flu-like symptoms such as fever, myalgias, and malaise

d. Acute HBV may also present with a serum sickness-like illness

e. Hepatitis C typically does not cause significant **acute** illness

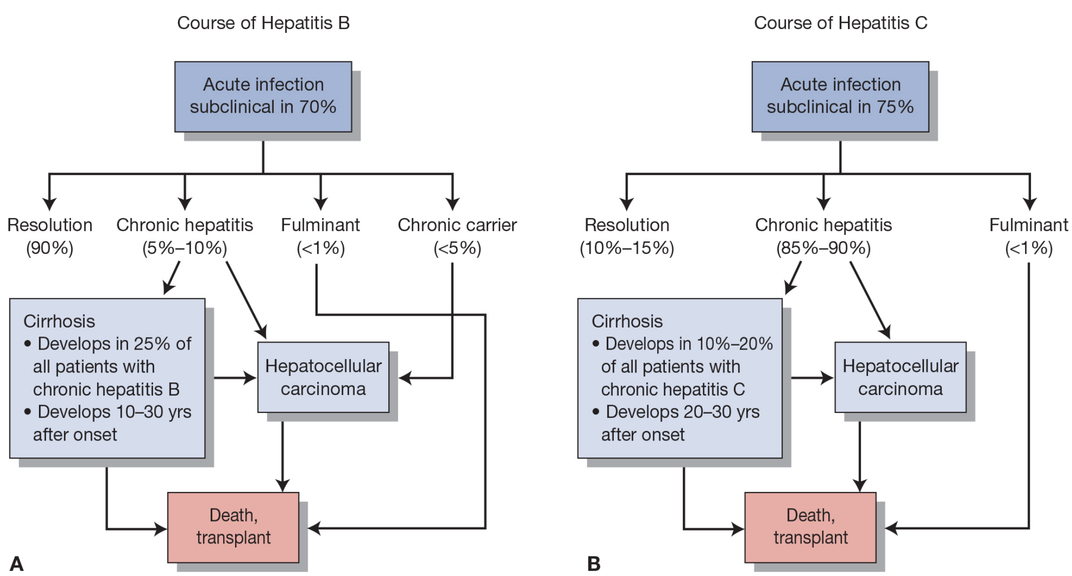


FIGURE 10-4 **A: Course of hepatitis B. B: Course of hepatitis C.**

Quick HIT

If transaminases are markedly elevated (>500), think of acute viral hepatitis, shock liver, or drug-induced liver injury.

3. Chronic hepatitis also has a wide variety of presentations. Some patients are asymptomatic (“chronic carriers”) and may only present with late complications of hepatitis, such as cirrhosis or hepatic cell carcinoma (HCC)

a. Chronic hepatitis occurs after acute hepatitis in 1% to 10% of patients with HBV and >80% patients with HCV

b. It is categorized based on the grade of inflammation, the stage of fibrosis, and the etiology of disease

c. The risk of developing cirrhosis or HCC is 25% to 40% in patients with chronic HBV and 10% to 25% in patients with chronic HCV

Quick HIT

Look for positive HBsAg and positive IgM anti-HBc to check for acute hepatitis B infection.

C. Diagnosis

1. Serum serology—the presence of serum antigens and immunoglobulins is the most important factor for diagnosing viral hepatitis. These are helpful for determining the acuity or chronicity of illness as well as adequate immunity (see Clinical Pearl 10-3).
2. PCR is used to detect viral RNA to diagnose HCV.
3. Hepatic panel—Elevation of serum transaminases is not diagnostic, but can be helpful.
   a. ALT (SGPT) is typically elevated more than AST (SGOT) for all forms of viral hepatitis (the opposite of alcoholic hepatitis).
   b. In acute hepatitis, ALT is usually >1,000. It is generally not as high as in drug-induced liver injury.
   c. In chronic HBV, ALT is usually mildly to moderate elevated, but can be >1,000 during exacerbations. In chronic HCV, ALT is generally normal or mildly elevated due to destruction of hepatocytes from longevity of disease.

CLINICAL PEARL 10-3

Hepatitis Serology

Hepatitis A

- Hepatitis A antibody (anti-HAV)
  - Anti-HAV is detectable during acute infection and persists for life, so its presence does not distinguish between active disease and immunity. IgM-specific antibody denotes acute infection.

Hepatitis B

- HB_sAg
  - Present in acute or chronic infection
  - Detectable as early as 1 to 2 weeks after infection
  - It persists in chronic hepatitis regardless of whether symptoms are present. If virus is cleared, then HB_sAg is undetectable
- Hepatitis B e antigen (HBeAg)
  - Reflects active viral replication, and presence indicates infectivity
  - Appears shortly after HB_sAg
- Anti-HB_sAg antibody (anti-HBs)
  - Present after vaccination or after clearance of HB_sAg—usually detectable 1 to 3 months after infection
  - In most cases, presence of anti-HBs indicates immunity to HBV
- Hepatitis B core antibody (anti-HBc)
  - Assay of IgM and IgG combined
  - Useful because it may be the only serologic marker of HBV infection during the "window period" in which HB_sAg is disappearing and anti-HB_sAg is not yet detectable
  - Does not distinguish between acute and chronic infection, and presence does not indicate immunity
- Viral load
  - HBV DNA measured by PCR; if it persists for more than 6 weeks, patient is likely to develop chronic disease

Hepatitis C

- Hepatitis C antibody
  - Key marker of HCV infection
  - Sometimes not detectable until months after infection, so its absence does not rule out infection
- Viral load: HCV RNA measured by PCR
  - Detectable 1 to 2 weeks after infection—more sensitive than HCV antibody

Hepatitis D

- Hepatitis D antibody (anti-HDV)
  - Presence indicates HDV superinfection
  - The antibody may not be present in acute illness, so repeat testing may be necessary

D. Treatment

1. Active (vaccine) and passive (immunoglobulin) immunization are available for both hepatitis A and B. It is the standard of care for infants and healthcare workers to be vaccinated for HBV (see Chapter 12).
2. Travelers often receive vaccinations for HAV. Passive immunization can be given for people who are exposed to the virus.
3. Treatment for hepatitis A and E is supportive.
4. Chronic HBV—treatment is indicated if high viral load or ALT elevation. Treat with nucleotide/nucleoside analogs (tenofovir, entecavir). Alternatively, treat with pegylated-interferon (peg-IFN).
5. Chronic HCV—all patients with detectable HCV viral level should be treated with antiviral agents with goal of cure.
   a. Interferon-free regimens: current standard of care with direct-acting antiviral agents (e.g., ledipasvir-sofosbuvir, glecaprevir-pibrentasvir, and many others). Treatment is expensive. Treatment regimen depends on stage of liver fibrosis, treatment history, and HCV genotype.
   b. Interferon-containing regimens: peginterferon and ribavirin. Less commonly used, as they have a high frequency of side effects, such as hematologic toxicity (neutropenia, thrombocytopenia, anemia), fatigue, flu-like symptoms, and neuropsychiatric symptoms.
6. Consider liver transplantation in advanced disease, although recurrence can occur after transplantation. Hepatitis C is the most common indication for liver transplantation in the United States.

Botulism

A. General Characteristics

1. Foodborne botulism results from ingestion of **preformed toxins** produced by spores of *Clostridium botulinum.* Improperly stored food

(e.g., home-canned foods) can be contaminated with these spores. Toxins can be inactivated by cooking food at high temperatures (e.g., 100°C [212°F] for 10 minutes).

2. Wound contamination is another source.
3. Inhalation botulism has been reported in laboratory workers but is not a common occurrence. Can be weaponized for bioterrorism.
4. Iatrogenic botulism can occur in patients who have received botulinum toxin for cosmetic procedures.

B. Clinical Features

1. The severity of illness ranges widely, from mild, self-limiting symptoms to rapidly fatal disease.
2. Abdominal cramps, nausea, vomiting, and diarrhea are common.
3. **The hallmark clinical manifestation is symmetric, descending flaccid paralysis.** It starts with dry mouth, diplopia, and/or dysarthria. Paralysis of limb musculature occurs later.

C. Diagnosis

1. The definitive diagnosis is identification of toxin in serum, stool, or gastric contents (bioassay).
2. Identifying *C. botulinum* alone in food is **not** a reliable diagnostic indicator.

***Quick* HIT**

Differential diagnosis of food-borne botulism includes:

- Guillain–Barré syndrome—characteristically ascending paralysis, but one variety (Miller Fisher variant) can be descending
- Lambert–Eaton syndrome
- Myasthenia gravis—EMG studies differentiate
- Diphtheria
- Tick paralysis

D. Treatment

1. Admit the patient and observe respiratory status closely. If foodborne botulism is suspected, can give laxatives or enemas if no signs of ileus.

2. If suspicion of botulism is high, administer botulinum antitoxin as soon as laboratory specimens are obtained (do not wait for the results).
3. For contaminated wounds—(in addition to the above) wound debridement and penicillin.

Intra-Abdominal Abscess

- Causes include spontaneous bacterial peritonitis, pelvic infection (e.g., tubo-ovarian abscess), pancreatitis, perforation of the GI tract, and osteomyelitis of the vertebral bodies with extension into the retroperitoneal cavity.
- Usually polymicrobial in origin.
- Diagnose using CT scan or ultrasound.
- Treatment typically involves drainage of the abscess.
- The antibiotic regimen should include broad coverage against gram-negative rods, enterococci, and anaerobes.

Clostridioides difficile Infection (CDI)

A. General Characteristics

1. This is also referred to as pseudomembranous colitis, although not all patients will have pseudomembranes.
2. Antibiotic treatment kills organisms that normally inhibit growth of *Clostridium difficile*, leading to overgrowth of *C. difficile* and toxin production.
3. Any antibiotic can predispose to CDI, but the most frequently implicated antibiotics are fluoroquinolones, clindamycin, broad-spectrum penicillins, and cephalosporins.
4. Symptoms usually begin within 2 weeks of antibiotic therapy. However, up to 10 weeks may elapse after stopping antibiotics before clinical findings become apparent. Community-acquired CDI can also occur in the absence of recent exposure to antibiotics.
5. Disease severity can be classified as nonsevere, severe, or fulminant depending on the WBC count, serum creatinine, and presence of hypotension/shock, ileus, or megacolon.

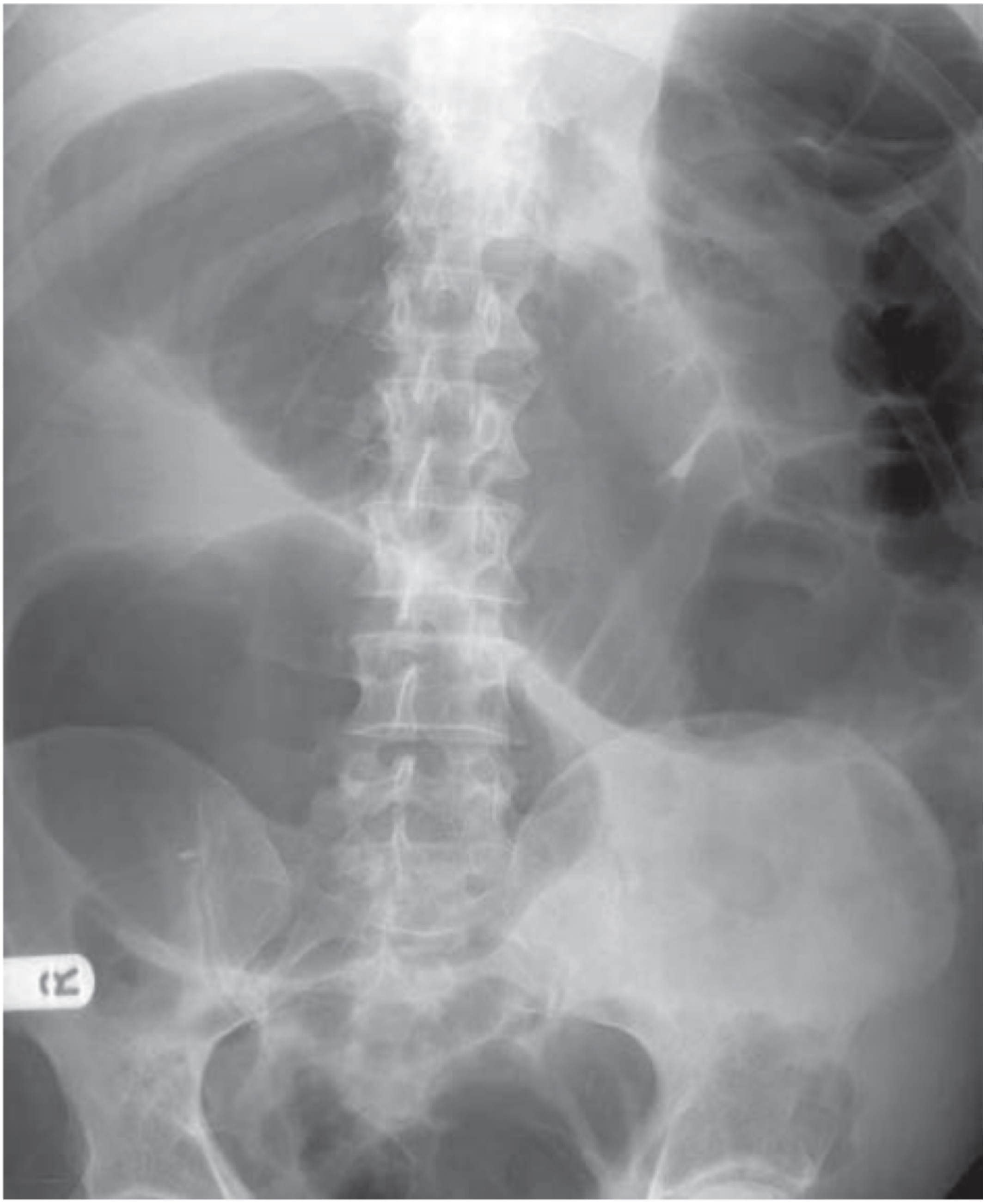


FIGURE 10-5 **Abdominal x-ray showing toxic megacolon in a patient with *C. difficile* enterocolitis.**
(Reprinted with permission from Marino PL. *Marino's The ICU Book: Print + Ebook with Updates*. 4th ed. Wolters Kluwer; 2013. Figure 40-3.)

Quick HIT

Complications of severe CDI that may require surgery:

- Toxic megacolon
- Colonic perforation or ischemia
- Abdominal compartment syndrome
- Progressive multiorgan failure

B. Clinical Features

1. Profuse watery diarrhea (≥3 loose stools in 24 hours), usually without blood or mucus
2. Crampy abdominal pain
3. Toxic megacolon (in severe cases) with risk of perforation (Figure 10-5)

C. Diagnosis

1. A positive *C. difficile* stool toxin PCR in the presence of diarrhea is diagnostic. Only liquid stool should be tested (as *C. difficile* toxin gene may be detected in the asymptomatic carrier state, which does not require treatment).
2. Stool anaerobic culture for *C. difficile* has high sensitivity, but results take several days.
3. Lower endoscopy is warranted only for selected cases where the diagnosis remains unclear and direct visualization of the bowel mucosa is needed.
4. Abdominal radiograph or CT of the abdomen/pelvis is indicated for severe or fulminant CDI to evaluate for toxic megacolon or other complications.
5. Leukocytosis is very common.

D. Treatment

1. Discontinue the offending antibiotic, if possible.
2. Supportive care for fluid resuscitation and electrolyte repletion.
3. Initial episode if nonsevere or severe: fidaxomicin or PO vancomycin. Fidaxomicin is preferred if available.

4. Initial episode if fulminant: PO vancomycin and IV metronidazole. If ileus is present, consider fecal microbiota transplantation or rectal vancomycin retention enema. Subtotal colectomy or diverting loop ileostomy with colonic lavage may be necessary.
5. First recurrence: fidaxomicin or PO vancomycin. If recurrence is within 6 months of prior infection, offer adjunct bezlotoxumab (monoclonal antibody that binds *C. difficile* toxin B) if available.
6. Second or subsequent recurrence: fidaxomicin, PO vancomycin with long taper, or fetal microbiota transplantation. Offer adjunct bezlotoxumab if available.
7. Regardless of choice of antibiotic, 15% to 35% of successfully treated patients will have recurrence within 2 to 8 weeks after stopping the antibiotic. Adjunct treatment with bezlotoxumab for recurrent CDI reduces recurrence risk, but has not been shown to reduce mortality and drug is costly.

Infections of the Genitourinary Tract

Cystitis (Lower Urinary Tract Infections)

A. General Characteristics

1. *Note that here and elsewhere in text, the terms "women" and "men" will be used, but recommendations for women extend to gender-diverse persons with female external genitalia at birth, and recommendations for men extend to gender-diverse persons with male external genitalia at birth.*
2. Cystitis is much more common in women than in men. Up to 33% of all women experience cystitis in their lifetime. The most common type is acute simple (uncomplicated) cystitis.
3. Simple or uncomplicated cystitis refers to infection limited to the bladder. When infection has extended beyond the bladder and there are features suggestive of systemic illness (e.g., fever, chills, flank pain), this is considered complicated UTI.

4. The majority of cases are caused by ascension of pathogens from the urethra to the bladder. These pathogens are from fecal flora that have colonized the area.
5. Common organisms.
   a. *E. coli* (most common)—causes 80% of cases.
   b. Other organisms—*Staphylococcus saprophyticus, Enterococcus, Klebsiella, Proteus* spp., *Pseudomonas, Enterobacter,* and yeast (such as *Candida* spp.)

Quick HIT

More than 90% of uncomplicated cystitis is caused by *E. coli, S. saprophyticus,* and *Enterococcus* spp. A small percentage is caused by *Proteus, Klebsiella, Enterobacter,* and *Pseudomonas.*

B. Risk Factors

1. Female genital anatomy—greater risk due to shorter urethral tract and distance from anus to urethra
2. Sexual intercourse
   a. Often the trigger of cystitis in women
   b. Use of diaphragms and spermicides further increases risk (alters vaginal colonization)
3. Pregnancy
4. Indwelling urinary catheters—risk factor for hospitalized patients
5. Personal history of recurrent UTIs
6. Host-dependent factors—increase risk for recurrent or complicated cystitis
   a. Diabetes mellitus
   b. Patients with spinal cord injury
   c. Immunocompromised state
   d. Any structural or functional abnormality that impedes urinary flow (e.g., incomplete voiding, neurogenic bladder, BPH, vesicoureteral reflux, calculi)
7. Male risk factors
   a. Uncircumcised males are at higher risk due to bacterial colonization of the foreskin

b. Insertive anal intercourse
c. Vaginal intercourse if colonized with uropathogens

Quick HIT

Noninfectious causes of cystitis or cystitis-like symptoms:
- Cytotoxic agents (e.g., cyclophosphamide)
- Radiation to the pelvis
- Dysfunctional voiding
- Interstitial cystitis

Quick HIT

Urine culture and sensitivity is usually the definitive diagnostic test. Acute simple cystitis in women can be treated based on urinalysis and presence of classic signs and symptoms alone.

C. Clinical Features

1. Dysuria—commonly expressed as burning on urination
2. Frequency
3. Urgency
4. Suprapubic tenderness
5. Gross hematuria is sometimes present
6. **In acute simple cystitis, fever and other systemic symptoms are characteristically absent**

Quick HIT

Asymptomatic Bacteriuria

- To diagnose asymptomatic bacteriuria, two successive positive cultures ($\geq 10^5$ CFU/mL) must be present.
- Treat asymptomatic bacteriuria only in pregnancy or before urologic surgery.

D. Diagnosis

1. Dipstick urinalysis

a. Positive urine leukocyte esterase test—presence of leukocyte esterase reflects pyuria
b. Positive nitrite test for presence of bacteria (gram-negative)—nitrite test is sensitive and specific for detecting Enterobacteriaceae and other nitrite-producing bacteria. But it lacks sensitivity for other organisms, so a negative test should be interpreted with caution
c. Combining the above two tests yields a sensitivity of 85% and specificity of 75%

Quick HIT

On UA, most important finding is white blood cells.

2. Urinalysis (clean-catch midstream specimen)
   a. Adequacy of collection
      - The presence of epithelial (squamous) cells indicates vulvar or urethral contamination
      - If contamination is suspected, perform a straight catheterization of the bladder
   b. Criteria for UTI (interpret in presence of symptoms, as these findings in the absence of symptoms only indicate symptomatic bacteriuria or pyuria)
      - Bacteriuria: ≥1 organism per oil-immersion field. Bacteriuria without WBCs may reflect contamination and is not a reliable indicator of infection
      - Pyuria is the most valuable finding for diagnosis: >10 leukocytes/μL is abnormal
   c. Other findings—hematuria and mild proteinuria may be present. Hematuria in and of itself does not require extended therapy
3. Urine Gram stain
   a. A count of $>10^5$ organisms/mL represents significant bacteriuria
   b. It is 90% sensitive and 88% specific
4. Urine culture
   a. Confirms the diagnosis (high specificity). Obtaining a urine culture is warranted if symptoms are not characteristic of cystitis, if a

complicated infection is suspected, if antimicrobial resistance is suspected, or if symptoms persist despite prior antibiotic treatment

b. Traditional criteria: $\geq 10^5$ CFU/mL of urine from a clean-catch sample; misses up to one-third of UTIs

c. Colony counts as low as 10^3 CFU/mL are adequate for diagnosis if clinical symptoms are present, especially if at risk for complicated UTI

5. Blood cultures—only indicated if patient is ill and systemic infection is suspected
6. IV pyelogram, cystoscopy, and excretory urography are not recommended unless structural abnormalities or obstruction is suspected

E. Complications

1. Complicated UTI
   a. Any UTI that spreads beyond the bladder (e.g., pyelonephritis, prostatitis, sepsis). Commonly presents with signs of infection beyond bladder (e.g., fever, chills, flank pain, costovertebral angle tenderness, perineal pain suggestive of prostatitis)
   b. Risk factors for upper UTI: pregnancy, diabetes, immunocompromising conditions, or urologic abnormalities
2. UTI during pregnancy—increased risk of preterm labor, low birth weight, and other complications, especially in advanced pregnancy
3. Recurrent infections
   a. Usually due to infection with new organism, but sometimes is a relapse due to unsuccessful treatment of the original organism
   b. Risk factors include impaired host defenses, pregnancy, vesicoureteral reflux, and sexual intercourse

Quick HIT

Complicated UTI refers to infection that has spread beyond the bladder. Some use the term "complicated UTI" to refer to UTI with the following factors (although this definition is not widely accepted):

- Men
- Diabetes mellitus
- Renal impairment
- Pregnancy
- Urinary tract obstruction, indwelling catheter, stent, nephrostomy tube, or recent instrumentation
- Antibiotic-resistant organism
- Recurrent infections
- Immunocompromised state (e.g., HIV, organ transplantation)

F. Treatment

1. Acute uncomplicated cystitis—most commonly in nonpregnant women. Several options exist:
   a. Oral TMP/SMX (Bactrim) for 3 days.
   b. Nitrofurantoin (5 to 7 days)—do not give if early pyelonephritis is suspected.
   c. Fosfomycin (single dose)—do not give if early pyelonephritis is suspected.
   d. Amoxicillin-clavulanate, cefpodoxime, or cefadroxil can be used alternatively if any of the above are not options.
   e. Avoid amoxicillin monotherapy due to high prevalence of antimicrobial resistance.
   f. Fluoroquinolones (ciprofloxacin in 3-day regimen) is a reasonable alternative to the above-mentioned agents. Try to avoid due to higher rates of adverse effects with fluoroquinolones.
   g. Treat presumptively for pyelonephritis if the condition fails to respond to a short course of antibiotics.
   h. Phenazopyridine (Pyridium) is a urinary analgesic; it can be given for 1 to 3 days for dysuria.

Quick HIT

For acute simple cystitis, empiric treatment is appropriate—do not wait for culture results.

Quick HIT

If complicated UTI, extend antibiotic treatment to 5 to 7 days.

2. Pregnant women with UTI
   a. Treat with amoxicillin, foxfomycin, or oral cephalosporins for 7 to 10 days.
   b. Avoid fluoroquinolones (can cause fetal arthropathy).
3. UTIs in men
   a. Treat as with uncomplicated cystitis in women, but consider longer duration (5 to 7 days) if concern for complicated UTI.
   b. Urologic workup is recommended in men with recurrent UTI, including evaluation for prostatic hypertrophy or other urinary tract obstruction.
4. Recurrent infections
   a. If relapse occurs within 3 months, check a urine culture to evaluate for antimicrobial resistance.
   b. Otherwise treat as for uncomplicated cystitis. If the patient has two or more UTIs within 6 months, consider antibiotic prophylaxis. However, must weigh risk of adverse effects and selection for resistant bacteria.
      - Postcoital prophylaxis in women with recurrent UTI: single dose of TMP/SMX or nitrofurantoin after intercourse or at first signs of symptoms.
      - Alternative low-dose prophylactic antibiotics (e.g., low-dose TMP/SMX) for 3-month trial.

Pyelonephritis

A. General Characteristics

1. Pyelonephritis is an infection of the upper urinary tract.
   a. It is usually caused by ascending spread from the bladder to the kidney
   b. Vesicoureteral reflux facilitates this ascending spread. See above for other risk factors
2. Organisms
   a. *E. coli* (most frequent cause).
   b. Other gram-negative bacteria include *Proteus, Klebsiella, Enterobacter,* and *Pseudomonas* spp.
   c. Gram-positive bacteria (less common) include *Enterococcus faecalis* and *S. aureus*
3. Complications
   a. Sepsis occurs in 10% to 25% of patients with pyelonephritis. May lead to shock.
   b. Emphysematous pyelonephritis—caused by gas-producing bacteria, typically in patients with diabetes mellitus and urinary tract obstruction
   c. Chronic pyelonephritis and scarring of the kidneys—rare unless underlying renal disease exists

B. Clinical Features

1. Symptoms
   a. Fever, chills
   b. Flank pain
   c. Symptoms of cystitis (may or may not be present)
   d. Nausea, vomiting, and diarrhea (sometimes present)
2. Signs
   a. Fever with tachycardia
   b. Patients generally appear more ill than patients with cystitis
   c. Costovertebral angle tenderness—unilateral or bilateral
   d. Abdominal tenderness may be present on examination

C. Diagnosis

1. Urinalysis
   a. Look for pyuria, bacteriuria, and **leukocyte casts**. Lack of pyuria suggests alternate diagnosis
   b. As in cystitis, hematuria and mild proteinuria may be present
2. Urine cultures—obtain in all patients with suspected pyelonephritis
3. Blood cultures—obtain if hospitalized or those with severe illness/sepsis
4. CBC—leukocytosis with left shift
5. Renal function—this is usually preserved. Impairment is usually reversible with IV fluids
6. Imaging studies—perform if severely ill, suspected urinary tract obstruction, or persistent symptoms despite 48 to 72 hours of appropriate antimicrobial therapy. Methods include renal ultrasound or CT of abdomen and pelvis

D. Treatment

1. For uncomplicated pyelonephritis
   a. Use outpatient treatment if the patient is not severely ill and can take oral antibiotics. Treat based on urine culture speciation and susceptibilities:
      - TMP/SMX for 14 days or a fluoroquinolone for 7 days is effective for most gram-negative rods.
      - Amoxicillin is appropriate for gram-positive cocci (enterococci, *S. saprophyticus*).
      - A single dose of ceftriaxone or gentamicin is often given initially before starting oral treatment.

   b. For those with hematuria on initial urinalysis, repeat urinalysis several weeks after treatment to evaluate for persistent hematuria.
   c. If symptoms fail to resolve within 48 hours, adjust treatment based on urine culture and consider imaging.
   d. Failure to respond to appropriate antimicrobial therapy after 48 to 72 hours suggests a functional or structural abnormality; perform CT of abdomen and pelvis.
2. If the patient is very ill, elderly, pregnant, unable to tolerate oral medication, or has significant comorbidities, or if sepsis is present:

a. Hospitalize and give IV fluids
b. Treat with antibiotics
- Start with parenteral antibiotics (broad-spectrum)—extended-spectrum cephalosporin, carbapenem, ciprofloxacin, or ampicillin PLUS gentamicin are common initial choices. Initial therapy should be guided by local resistance data and tailored once organism is isolated
- If blood cultures are negative, treat with IV antibiotics until the patient is afebrile for 24 hours, then give oral antibiotics to complete a 7- to 14-day course. Total duration depends on clinical response, chosen antibiotic, and whether complicating factors are present or not.
- If blood cultures are positive (bacteremia due to UTI), treat with IV antibiotics initially. If uncomplicated bacteremia due to Enterobacteriaceae, and appropriate clinical response to initial therapy, can switch to oral agent and treat for a total 7- to 14-day course. A shorter course (7 days instead of 14) may be preferred in selected cases.

3. For recurrent pyelonephritis
a. Treat with antimicrobials. Use urine culture to guide directed therapy.
b. Evaluate for underlying urinary tract abnormality or obstruction, such as neurogenic bladder or indwelling device (e.g., urinary stent). Consider urology or gynecology consultation.

Prostatitis

A. General Characteristics

1. Acute bacterial prostatitis
a. Less common than chronic bacterial prostatitis
b. Occurs more commonly in younger men
c. Pathophysiology
- Ascending infection from the urethra and reflux of infected urine
- May occur after urinary catheterization
- Other causes—direct or lymphatic spread from the rectum
- Hematogenous spread (rare)

d. Gram-negative organisms predominate (e.g., *E. coli, Klebsiella, Proteus, Pseudomonas, Enterobacter,* and *Serratia* spp.). If *Staphylococcus* is isolated, evaluate for endovascular staphylococcal infection

Quick HIT

Acute Versus Chronic Prostatitis

- Acute prostatitis is a more serious condition than chronic prostatitis, and urgent treatment is necessary.
- Acute prostatitis is much more obvious clinically (fever, exquisitely tender prostate), whereas chronic prostatitis is difficult to diagnose because the prostate may not be tender and findings are variable.

2. Chronic bacterial prostatitis
   a. More common than acute bacterial prostatitis; true prevalence is difficult to determine because many cases are asymptomatic and are diagnosed incidentally
   b. It most commonly affects men 40 to 70 years of age
   c. It has the same routes of infection as acute bacterial prostatitis. It may develop from acute bacterial prostatitis
   d. Organisms are similar to those in acute prostatitis

Quick HIT

Avoid vigorous prostatic massage in patients with acute bacterial prostatitis because it may induce bacteremia.

B. Clinical Features

1. Acute prostatitis
   a. Fever, chills—patients may appear toxic.
   b. Irritative voiding symptoms—dysuria, frequency, and urgency are common.
   c. Perineal pain, low back pain, and urinary retention may be present as well.
2. Chronic prostatitis

a. Patients may be asymptomatic. Patients do not appear ill. Fever is uncommon.
b. Patients frequently have recurrent UTIs with irritative voiding and/or obstructive urinary symptoms.
c. There is dull, poorly localized pain in the lower back, perineal, scrotal, or suprapubic region.

C. Diagnosis

1. DRE—there is a boggy, exquisitely tender prostate in acute disease. In chronic disease, prostate is enlarged and usually nontender.
2. Urinalysis—numerous (sheets of) WBCs are present in acute bacterial prostatitis.
3. Urine cultures—almost always positive in acute prostatitis.
4. Chronic prostatitis—the presence of WBCs in expressed prostatic secretions suggests diagnosis. Urine cultures may be positive (chronic bacterial prostatitis) or negative (chronic nonbacterial prostatitis).
5. Obtain CBC and blood cultures if patient appears toxic or if sepsis is suspected.
6. Prostate-specific antigen (PSA) can be elevated in acute prostatitis.

***Quick* HIT**

Recurrent exacerbations are common in chronic prostatitis if not treated adequately. Recurrent UTI is very common in these patients.

D. Treatment

1. Acute prostatitis.
   a. If it is severe and the patient appears toxic, hospitalize the patient and initiate IV antibiotics.
   b. If it is mild, treat on an outpatient basis with antibiotics—TMP/SMX or a fluoroquinolone and doxycycline. Treat for 4 to 6 weeks.
   c. The patient usually responds to therapy.
2. Chronic prostatitis.
   a. Treat with a fluoroquinolone or TMP/SMX. For chronic bacterial prostatitis, a prolonged course (at least 6 weeks) is recommended but does not guarantee complete eradication.

b. It is very difficult to treat. Recurrences are common.

Quick HIT

Eighty percent of cases of reactive arthritis are associated with chlamydial infection.

Sexually Transmitted Diseases

Condyloma Acuminata (Anogenital Warts)

- These are caused by HPV.
- **They are the most common** sexually transmitted infection **(STI).**
- **See** Chapter 11, Common Dermatologic Problems, Inflammatory, Allergic, and Autoimmune Skin Conditions, Warts.

Quick HIT

Chlamydia infection is a risk factor for cervical cancer, especially when there is a history of multiple infections.

Chlamydia

A. General Characteristics

1. **Chlamydia is the most common bacterial STI.** The organism is an intracellular pathogen.
2. Many patients are coinfected with gonorrhea.
3. The incubation period is 5 to 14 days after infection.

B. Clinical Features

1. Many cases are asymptomatic (80% of women, 50% of men).

2. Men or individuals with a penis and testes who are symptomatic may have any of the following: dysuria, purulent urethral discharge, scrotal pain and swelling, proctitis, and fever.
3. Women or individuals with a cervix who are symptomatic may have purulent urethral discharge, intermenstrual or postcoital bleeding, proctitis, and dysuria.
4. Syndromes common to all: conjunctivitis, pharyngitis, reactive arthritis, and genital lymphogranuloma venereum.

Quick HIT

Complications of Chlamydia

- Complications in men include epididymitis and proctitis.
- Complications in women include pelvic inflammatory disease, salpingitis, tubo-ovarian abscess, ectopic pregnancy, and Fitz-Hugh–Curtis syndrome. **Chlamydia is a leading cause of infertility in women due to tubal scarring.**

C. Diagnosis

1. Diagnostic tests include culture, enzyme immunoassay, and molecular tests such as nucleic acid amplification testing (NAAT). Serologic tests are not used for *Chlamydia.*
2. NAAT tests have replaced cultures as the screening test of choice due to higher sensitivity.
3. Patients should also be tested for gonorrhea due to high rates of coinfection.

D. Treatment

1. Doxycycline (oral for 7 days) is preferred in nonpregnant individuals. Azithromycin (oral one dose) is another option but should be reserved for those who are unable to complete the 7-day course of doxycycline, or for pregnant individuals.
2. Treat all sexual partners.

Quick HIT

In gonorrhea, infection of the pharynx, conjunctiva, and rectum can occur.

Gonorrhea

A. General Characteristics

1. The responsible organism is *Neisseria gonorrhoeae* (a gram-negative, intracellular diplococcal organism).
2. Gonorrhea is usually asymptomatic in women but symptomatic in men. Therefore, complications occur more often in women due to undetected disease.
3. It is almost always transmitted sexually (except with neonatal transmission).
4. Coinfection with *Chlamydia trachomatis* occurs in 30% of patients (more common in women).

Quick HIT

Gonorrheal Complications

- Pelvic inflammatory disease, with possible infertility and chronic pelvic pain
- Epididymitis, prostatitis (uncommon)
- Salpingitis, tubo-ovarian abscess
- Fitz-Hugh–Curtis syndrome (perihepatitis)—RUQ pain; elevated transaminases
- Disseminated gonococcal infection

B. Clinical Features

1. Men
   a. Gonorrhea is asymptomatic in up to 10% of carriers. These asymptomatic carriers can still transmit the disease
   b. Most men have symptoms involving the urethra—for example, purulent discharge, dysuria, erythema and edema of urethral meatus, and frequency of urination

2. Women
   a. **Most women are asymptomatic or have few symptoms**
   b. Women may have symptoms of cervicitis or urethritis—for example, purulent discharge, dysuria, intermenstrual bleeding, and dyspareunia
3. Disseminated gonococcal infection (occurs in 1% to 3% of patients)—possible findings:
   a. Fever, arthralgias, tenosynovitis (of hands and feet)
   b. Migratory polyarthritis/septic arthritis, endocarditis, or even meningitis
   c. Skin rash (usually on distal extremities)

C. Diagnosis

1. NAAT is the diagnostic test of choice.
2. Gram stain and culture of urethral discharge or endocervical sample showing organisms within leukocytes is highly specific for gonorrhea.
3. Obtain NAAT testing in all cases—from the urethra or cervix. Obtain swabs from other areas (oral, rectal) depending on sexual history. A culture is useful when there is concern for antimicrobial resistance. Treat empirically because culture results take 1 to 2 days to return.
4. If testing for gonorrhea, cotest for chlamydia due to high rates of coinfection. Also offer testing for HIV and syphilis.
5. Obtain blood cultures if disease has disseminated.

A 26-year-old woman presents to her physician with multiple complaints. Two days ago, she noticed fevers, chills, and malaise. One day ago, she developed pain in her left knee, left ankle, and right elbow; in addition, there is pain and swelling over her hands. She denies any other medical problems, recent upper respiratory tract infections or diarrheal illnesses, and does not smoke or use illicit drugs. She is sexually active and has had several new partners in the last few months. She is examined, which is significant for pain to palpation over the tendons in her hand and wrist, multiple scattered hemorrhagic vesicles and pustules over the dorsal aspects of both forearms, and erythema and swelling of her left knee, left ankle, and right elbow with decreased range of motion at these joints.

Which of the following is the most likely diagnosis?

A. Reactive arthritis
B. Infective endocarditis
C. Disseminated *Neisseria gonorrhoeae*
D. *Neisseria meningitidis* infection

- **The answer is C: Disseminated *Neisseria gonorrhoeae*.** This young, sexually active patient is presenting with systemic symptoms, tenosynovitis, pustular skin lesions, and polyarthritis, which suggests the diagnosis of disseminated gonococcal infection. This infection can present with the symptoms seen in this vignette, or with purulent arthritis without cutaneous manifestations. **(A)** Reactive arthritis may develop in response to a diarrheal illness or a *Chlamydia trachomatis* infection; it can also present with oligoarthritis but also commonly presents with uveitis and urethritis. Reactive arthritis is less likely to have cutaneous manifestations. **(B)** There is no mention of a cardiac murmur, and this patient does not meet the modified Duke criteria for the diagnosis of infective endocarditis. **(D)** *N. meningitidis*

infection can present similarly, but typically has more severe systemic symptoms (with or without meningitis).

D. Treatment

1. Ceftriaxone (IM, one dose) is preferred because it is also effective against syphilis. Other options include oral cefixime or azithromycin plus gentamicin. There are rising rates of antibiotic resistance to fluoroquinolones.
2. Also give doxycycline (for 7 days, preferred agent) or azithromycin (one dose) to cover coexistent chlamydial infection.
3. If disseminated, hospitalize the patient and initiate ceftriaxone (IV or IM for 7 days).

Quick HIT

It is important (but often difficult) to identify patients with primary HIV infection because of the benefits of early antiretroviral therapy. A high index of suspicion is necessary.

HIV and AIDS

A. General Characteristics

1. Pathophysiology
   a. The most common virus associated with HIV is the HIV type 1 human retrovirus
   b. The virus attaches to the surface of CD4+ T lymphocytes (targets of HIV-1); it enters the cell and uncoats, and its RNA is transcribed to DNA by reverse transcriptase
   c. Billions of viral particles are produced each day by activated CD4 cells. When the virus enters the lytic stage of infection, CD4 cells are destroyed. It is the depletion of the body's arsenal of CD4 cells that weakens host **cellular immunity**
2. Transmission is usually sexual or parenteral. Other than semen and blood, fluids that transmit the disease are breast milk and vaginal fluid

a. Risk of transmission:
   - Needlestick injury—1 in 500
   - Needle-sharing during injection drug use—1 in 200
   - Receptive penile-vaginal intercourse—1 in 1,000
   - Insertive penile-vaginal intercourse–1 in 3,000
   - Receptive anal intercourse—1 in 100
   - Insertive anal intercourse—1 in 1000
   - Mother to child—one in three without medications. With medications, risk is under 2 in 100

b. Cesarean delivery is indicated if viral load is over 1,000 copies/mL. If CD4 count is high (over 500) and viral load is low (under 1,000), C-section is not necessary

3. Mortality has become much less common with widespread use of antiretroviral therapy (ART). For those who start treatment early and maintain consistent use of ART, lifespan is near-normal. When premature death occurs, usually in absence of effective ART, it is often secondary to opportunistic infection, wasting, or cancer
4. Risk factors: engaging in unprotected anal intercourse, IV substance use, receipt of blood transfusion before 1985 (before widespread screening of donor blood), sexual contact with HIV-positive individuals, being born to mothers who are HIV positive

CLINICAL PEARL 10-4

HIV Serology

CD4 Cell Count

- It is the best indicator of the status of the immune system and of the risk for opportunistic infections and disease progression. However, level can be affected by acute illness and medications that suppress the bone marrow.
- It is used to determine when to initiate antiretroviral therapy and PCP prophylaxis. It is also useful in assessing the response to antiretroviral therapy.
- If untreated (no antiretroviral therapy), the CD4 cell count decreases at an average rate of about 50 per year.
- If >500, the immune system is essentially normal. HIV-related infection or illness is unlikely.
- If 200 to 500, there is an increased risk of HIV-related problems, such as herpes zoster, TB, lymphoma, bacterial pneumonias, and Kaposi sarcoma. However, many patients are asymptomatic at these CD4 levels.
- Most opportunistic infections occur when the CD4 count falls below 200.

Viral Load (HIV-1 RNA Levels)

- Used to assess response to and adequacy of antiretroviral therapy; provides complementary prognostic information to the CD4+ count.
- If the viral load is still >50 after about 4 months of treatment, modification in the regimen may be needed.
- Do not stop antiretroviral therapy even if viral loads are undetectable for years. Latently infected cells can lead to reappearance of viral RNA once therapy is stopped.
- Measure the plasma HIV RNA levels and the CD4 cell count at the time of diagnosis and every 3 to 4 months thereafter.

B. Clinical Features

1. Stage 1: Acute HIV infection (see also Clinical Pearl 10-4)
    a. May present with a mononucleosis-like syndrome about 2 to 4 weeks after exposure to HIV. Duration of the illness is brief (3 days to 2 weeks).
    b. Often asymptomatic (seropositive, but no clinical symptoms of HIV infection).
    c. Symptoms include fever, sweats, malaise, lethargy, headaches, arthralgias/myalgias, diarrhea, sore throat, lymphadenopathy, and a generalized maculopapular rash.

2. Stage 2: Chronic HIV infection without AIDS
   a. Following early infection, period of stability of viral level. Usually asymptomatic.
   b. CD4 counts are normal (>500/mm^3) but begin to decline.
   c. Longest phase (lasts 8 to 10 years, but varies widely, especially with treatment).
   d. If left untreated, as CD4 counts decline, patients may develop the following symptoms:
      - Persistent generalized lymphadenopathy.
      - Localized fungal infections (e.g., on fingernails, toes, oral or esophageal thrush).
      - Recalcitrant vaginal yeast and trichomonal infections in women.
      - Oral hairy leukoplakia on the tongue.
      - Skin manifestations including seborrheic dermatitis, psoriasis exacerbations, molluscum, and warts.
      - Constitutional symptoms (night sweats, weight loss, and diarrhea).

Quick HIT

The course of HIV varies considerably from patient to patient. However, the typical course can be divided into the following three phases: acute HIV, chronic HIV, and AIDS.

3. Stage 3: Acquired immunodeficiency syndrome (AIDS)
   a. Final and most severe stage of HIV infection that occurs if HIV is left untreated.
   b. Marked immune suppression leads to disseminated opportunistic infections and malignancies.
   c. CD4 count is <200 cells/mm^3.
   d. Pulmonary, GI, neurologic, cutaneous, and systemic symptoms are common (see Table 10-3).

C. Diagnosis

1. PCR RNA viral load test—patients with acute HIV infection have very high levels of viremia. This test is repeated to assess effectiveness of

therapy. Detectable viremia does not develop until 10 to 15 days after infection. This is test of choice to confirm acute HIV infection.

2. p24 antigen assay—newer assays have excellent sensitivity and will become positive approximately 5 to 7 days after viral RNA is detectable.
3. Enzyme-linked immunosorbent assay (ELISA) method: detects HIV antibodies. Seroconversion occurs 3 to 7 weeks after infection.
4. Preferred testing approach: fourth generation antigen/antibody combination HIV-1/2 immunoassay. Tests for IgM, IgG, and p24 antigen.
   - Combined testing for both antigen/antibody has excellent sensitivity (p24 antigen is detectable before antibody seroconversion in acute infection).
   - A negative ELISA combined with p24 antigen essentially excludes HIV (99% sensitive) if the patient has not had a subsequent exposure before testing.
   - If positive, a HIV-1/HIV-2 antibody differentiation immunoassay can be done to determine whether infection is with HIV-1, HIV-2, or both
   - Western blot is sometimes done to confirm a positive ELISA to exclude possibility of false-positive screening test. This is usually not done any longer due to availability and timeliness of fourth-generation testing above.
5. Diagnosis of AIDS.
   a. Definition: A patient with HIV has AIDS if they have (1) a CD4+ T-cell count <200 cells/μL, or (2) an AIDS-defining condition. (See Table 10-4.)

Quick HIT

The combination of ELISA and p24 antigen testing yields an overall sensitivity and specificity of >99%.

D. Treatment

1. Antiretroviral therapy (Table 10-5)
   a. Indications

- All patients with HIV, regardless of CD4 count
- Daily oral pre-exposure prophylaxis (PrEP) is recommended as prevention for those at high risk of infection

b. Triple-drug regimens known as ART: To target and prevent HIV replication at three different points along the replication process, use two nucleoside reverse transcriptase inhibitors and either of the following:
- An integrase strand transfer inhibitor (INSTI, e.g., elvitegravir, bictegravir)
- A nonnucleoside reverse transcriptase inhibitor (NNRTI)
- Protease inhibitor with a pharmacokinetic booster (e.g., ritonavir, cobicistat)
- There are many different combinations. Treatment choice must take into account pregnancy status, toxicity, pill burden, drug-drug interactions, access, cost, among many factors
- New data support the use of a two-drug regimen dolutegravir/lamivudine in some patients

c. Monitor the response to treatment using plasma HIV RNA load—the goal is to reduce the viral load to undetectable levels

d. ART should be continued during pregnancy to reduce risk of vertical transmission and treat maternal HIV disease

***Quick* HIT**

Antiretroviral Therapy in HIV

- The importance of adherence to ART cannot be overemphasized, because even minor deviations may result in drug resistance. This has been improved in recent years by combining the medications into a single pill for patients.
- Other options for patients at risk for poor adherence are to select a regimen with high barrier to resistance. Avoid two-drug regimen for patients with adherence concerns.

TABLE 10-3 Clinical Manifestation of AIDS

System	Condition	Comments
Pulmonary	Community-acquired bacterial pneumonia	Recurrent bacterial pneumonia (two or more episodes per year) is 20 times more common in HIV-1 patients with low CD4 cell counts (<200/mm^3) than in those with normal counts
	Pneumocystic pneumonia	• Seventy percent of patients acquire PJP at some point; often the initial opportunistic infection establishes the diagnosis of AIDS • **Leading cause of death in patients with AIDS** • **Occurs when CD4 count is 200** • Clinical findings: fever, nonproductive cough, shortness of breath (with exertion at first, then occurring at rest) • CXR: diffuse interstitial infiltrates; negative radiographs in 10–15% of patients with PCP • Treatment: TMP-SMX (PO or IV) for 3 wk; steroid therapy if patient is hypoxic or has elevated A–a gradient • Prophylaxis: Oral TMP-SMX, 1 dose daily, is recommended
	Tuberculosis (other infections)	Negative PPD and IGRA test results are frequent among AIDS patients due to immunosuppression • CMV or MAC: **increased risk when the CD4 count <50** • *C. neoformans, Histoplasma capsulatum,* neoplasms (Kaposi sarcoma)
Nervous system	HIV-associated dementia	• Progressive process in 33% of patients • Occurs primarily in untreated patients with advanced HIV • Characterized by deficits in memory, executive functioning, attention, and concentration; apathy; and psychomotor slowing
	Toxoplasmosis	• Usually a reactivation of latent infection of *Toxoplasma gondii* • Symptoms both of a mass lesion (discrete deficits, headache) and of encephalitis (fever, altered mental status) • CT scan or MRI shows characteristic findings: multiple (more than three) **contrast-enhanced mass lesions in the basal ganglia and subcortical white matter** though single lesions are possible

	Cryptococcal meningitis	• Diagnosed by identifying organisms in CSF by cryptococcal antigen, culture, or **staining with India ink** • Treat with liposomal amphotericin B plus flucytosine for 14 days. Follow this with 8 wk of oral fluconazole. Long-term suppression therapy with oral fluconazole is needed (at least 1 yr, can be lifelong)
	Other CNS infections	Bacterial meningitis, histoplasmosis, CMV, progressive multifocal leukoencephalopathy (PML), HSV, neurosyphilis, TB
	Noninfectious CNS diseases	CNS lymphoma, CVA, metabolic encephalopathies
Gastrointestinal	Diarrhea	Most common GI complaint; caused by a variety of pathogens (*E. coli, Shigella, Salmonella, Campylobacter, CMV, Giardia, Cryptosporidium, Isospora belli, Mycobacterium avium-intracellulare*). Antibiotic therapy is also a common cause
	Oral lesions	Oral thrush (candidiasis; scrapable), HSV or CMV (ulcers), oral hairy leukoplakia (EBV infection; nonscrapable), Kaposi sarcoma
	Esophageal involvement	Candidiasis is most common cause of dysphagia; also CMV and HSV—**seen with CD4 counts <100**
	Anorectal disease	Proctitis—*N. gonorrhoeae, C. trachomatis,* syphilis, HSV
Dermatologic	Kaposi sarcoma	• More common in men who have sex with men than in other groups • Painless, raised brown-black or purple papules (common sites: face, chest, genitals, oral cavity) • Widespread dissemination can occur
	Infections	HSV infections, molluscum contagiosum, secondary syphilis, warts, shingles, and many other skin conditions/infections occur with higher frequency
Miscellaneous	CMV infection	• Common cause of serious opportunistic viral disease • Disseminated disease is common and usually involves the GI or pulmonary systems • Most important manifestation is retinitis—unilateral visual loss that can become bilateral if untreated (seen in 5–10% of AIDS patients) • Colitis and esophagitis are other findings • Treat with ganciclovir or foscarnet

Mycobacterium avium complex (MAC)	• Most common opportunistic bacterial infection in AIDS. Wasting syndrome (weight loss, fever), lymphadenopathy, anemia • MAC causes disseminated disease in 50% of AIDS patients. MAC occurs in patients with advanced AIDS and fewer than 50 CD4 cells • Diarrhea and weight loss are constitutional symptoms
HIV-1 wasting syndrome	Profound involuntary loss of more than 10% of body weight in conjunction with **either** of the following: • Chronic diarrhea (two or more stools per day for more than 1 mo) • Fever and persistent weakness for a similar period in the absence of another cause
Malignancies	• Kaposi sarcoma • Non-Hodgkin lymphoma—rapidly growing mass lesion in CNS • Primary CNS lymphoma

TABLE 10-4 AIDS-defining Conditions

Candidiasis, of bronchi, trachea, lungs, or esophagus
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis of >1 mo duration
Cytomegalovirus disease outside lymphoreticular system
Cytomegalovirus retinitis, with loss of vision
Encephalopathy, HIV-related
Herpes simplex infection of >1 mo duration or visceral herpes simplex
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis of >1 mo duration
Kaposi sarcoma
Lymphoma: primary central nervous system, immunoblastic, or Burkitt's
Mycobacterial disease, disseminated or extrapulmonary
M. tuberculosis infection of any site
Pneumocystis jirovecii pneumonia
Pneumonia, recurrent (more than one episode in 1 yr)
Progressive multifocal leukoencephalopathy
Salmonella bacteremia, recurrent
Toxoplasmosis, cerebral
Wasting syndrome due to HIV

Modified with permission from Stoller JK, Ahmad M, Longworth DL. *The Cleveland Clinic Intensive Review of Internal Medicine*. 3rd ed. Lippincott Williams & Wilkins; 2002:188. Table 15.6.

TABLE 10-5 Antiretroviral Therapy

Drug	Mechanism	Toxicity
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Tenofovir alafenamide (TAF) Tenofovir disoproxil fumarate (TDF) (only nucleotide) Zidovudine (ZDV, formerly AZT)	Competitively inhibit reverse transcriptase by lacking 3′ OH group. All are nucleosides and require phosphorylation to be active except tenofovir. ZDV used in pregnancy.	Mitochondrial toxicity (lactic acidosis, peripheral neuropathy, pancreatitis, lipoatrophy, hepatic steatosis), bone marrow suppression (ZDV)
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz (EFV, contraindicated in pregnancy) Etravirine (ETR) Nevirapine (NVP) Rilpivirine (RPV)	Noncompetitively inhibit reverse transcriptase. Do not require phosphorylation.	Rash and hepatotoxicity. CNS symptoms and QT prolongation with ETR and RPV.
Protease Inhibitors		
Atazanavir (ATV) Atazanavir-cobicistat (ATV/COBI) Darunavir (DRV) Darunavir-cobicistat (DRV/COBI) Fosamprenavir (FPV) Indinavir (IDV, crystal-induced nephropathy) Lopinavir/ritonavir (LPV/r) Nelfinavir (NFV) Ritonavir (RTC, "boost" by inhibiting P450) Saquinavir ("boost" by inhibiting P450)	Inhibited protease (*pol* gene), which cleaves polypeptide products. All end in -navir.	Hyperglycemia, hyperlipidemia, GI intolerance, lipodystrophy

Tipranavir (TPV)		
Integrase Strand Transfer Inhibitors (INSTI)		
Raltegravir (RAL) Elvitegravir (EVG) Dolutegravir (DTG) Cabotegravir (CAB) Bictegravir (BIC)	Inhibit integration into host cell.	Insomnia, dizziness, weight gain
Fusion Inhibitors		
Enfuvirtide Maraviroc	Binds gp41, inhibits entry. Binds CCR–5, inhibits interaction with gp120.	Skin reaction at injection site

2. Opportunistic infection prophylaxis
   a. Pneumocystic pneumonia (PCP), formerly *P. carinii,* now named *Pneumocystis jirovecii*
      - Occurs in patients with HIV not taking ART, or when CD4 cell count is <200 cells/μL and patient is not on prophylaxis
      - Dyspnea, dry cough, fever
      - Tests: CXR (bilateral interstitial infiltrates), high-resolution CT chest (patchy or nodular ground-glass opacities), LDH level (always elevated), ABG (hypoxia or increased A–a gradient), sputum stain for pneumocystis (very specific but not sensitive), bronchoscopy with BAL (most accurate test)
      - TMP/SMX is the preferred agent for both treatment and prophylaxis
   b. TB
      - Screen all patients at initial presentation with PPD test or IGRA. Screening thereafter is determined by presence of TB risk factors
      - Treat for latent TB if screening test is positive. Note that if CD4 cell count <200 cells/μL, IGRA may be indeterminate or false negative and should be repeated once CD4 cell count has increased above threshold
   c. Atypical mycobacteria—*Mycobacterium avium* complex (MAC)
      - Start prophylaxis when CD4 cell count is <50 and if patient is not on ART
      - Previously recommended to start prophylaxis for all patients with CD4 cell count <100, but risk of MAC infection is low with new

ART drugs
  - Clarithromycin and azithromycin are prophylactic agents
d. Toxoplasmosis
  - Start prophylaxis when CD4 count is <100
  - TMP/SMX is the preferred agent
3. Vaccination **(no live-virus vaccines!)**
   a. Pneumococcal polysaccharide vaccine (PPSV23) and 13-valent conjugate vaccine (PCV13)
   b. Influenza vaccine—annual
   c. Hepatitis A and B vaccine (if not already antibody-positive) (See Chapter 12.)
   d. Meningococcal vaccine—every 5 years
   e. Human papillomavirus vaccine (HPV)—ages 13 through 26 years

Herpes Simplex

A. General Characteristics

1. There are two types of HSV: HSV-1 and HSV-2. Both are very prevalent in the general population (Figure 10-6).
   a. HSV-1 is typically associated with lesions of the oropharynx.
   b. HSV-2 is associated with lesions of the genitalia (see Table 10-6).
   c. Both viruses, however, can cause either genital or oral lesions.
2. Pathophysiology: After inoculation, the HSV replicates in the dermis and epidermis, then travels via sensory nerves up to the dorsal root ganglia. It resides as a latent infection in the dorsal root ganglia, where it can be reactivated at any time and reach the skin through peripheral nerves.
3. Transmission
   a. HSV is transmitted by contact with people who have active ulcerations or shedding of virus from mucous membranes. HSV-1 is typically associated with transmission through nonsexual personal contact (e.g., kissing), and HSV-2 through sexual contact.
   b. Most people acquire HSV-1 in childhood, and more than 80% of adults have been infected with HSV-1.
   c. Episodes of genital herpes frequently may be asymptomatic or may produce symptoms that often go unrecognized. Virus is still shed,

and the infected person is contagious.

d. Contracting one form of herpes confers some degree of cross-immunity, rendering primary infection with the other form of herpes less severe.
e. Infection with genital herpes is associated with an increased risk of contracting HIV.

B. Clinical Features

1. HSV-1
   a. Primary infection is usually asymptomatic and often goes unnoticed.
   b. When symptomatic, primary infection is associated with systemic manifestations (e.g., fevers, malaise) as well as oral lesions (described below).
   c. Oral lesions involve groups of vesicles on patches of erythematous skin. Herpes labialis (cold sores) are most common on the lips (usually painful, heal in 2 to 6 weeks).
   d. HSV-1 is also associated with Bell palsy.

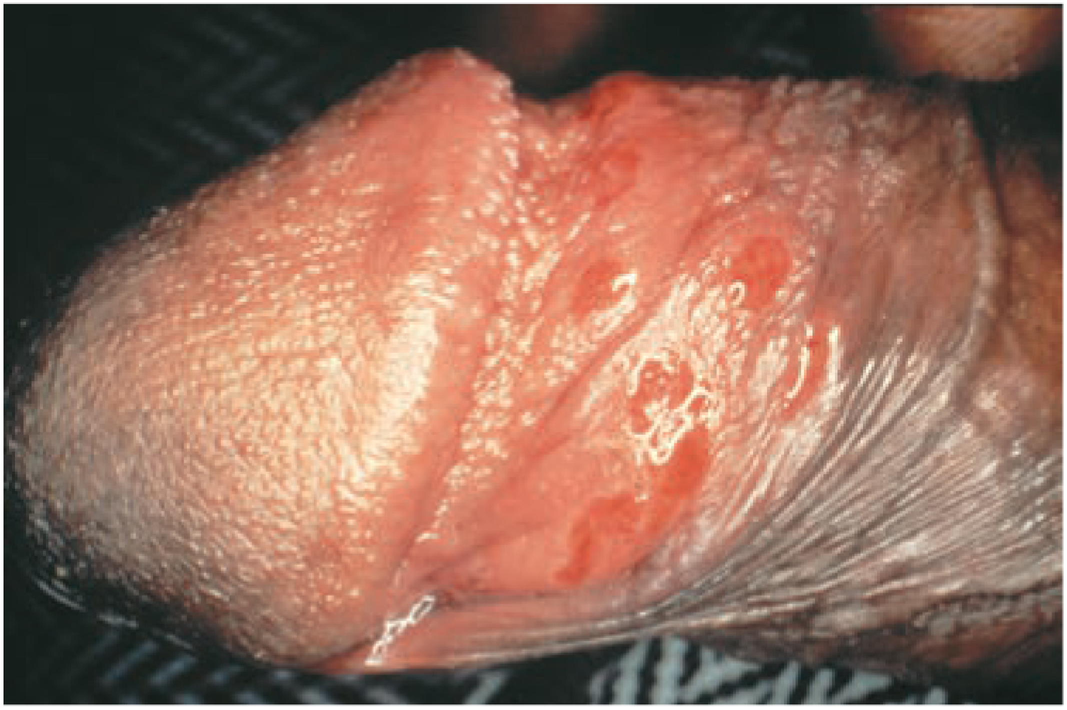


FIGURE 10-6 **Herpes simplex virus.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 19.13.)

TABLE 10-6 Clinical Manifestations of Genital Ulcers With Regional Lymphadenopathy

Genital Lesions	Incubation (Days)	Type	Pain	Number	Duration
Primary syphilis	3–90	Clean ulcer, raised	No	Usually single	3–6 wk
Primary herpes simplex virus	1–26	Grouped papules, vesicles, pustules, ulcers	Yes	Often multiple	1–3 wk
Chancroid	1–21	Purulent ulcer, shaggy border	Yes	Single in men, multiple in women	Progressive
Lymphogranuloma venereum	3–21	Papule, vesicle, ulcer	No	Usually single	Few days
Granuloma inguinale	8–80	Nodules, coalescing granulomatous ulcers	No	Single or multiple	Progressive
Inguinal Adenopathy	**Onset**	**Pain**	**Type**	**Frequency**	**Constitutional Symptoms**
Primary syphilis	Same time	No	Firm	80%, 70% bilateral	Absent
Primary herpes simplex virus	Same time	Yes	Firm	80%, usually bilateral	Common
Chancroid	Same time	Yes	Fluctuant, may fistulize	50–65%, usually unilateral	Uncommon
Lymphogranuloma venereum	2–6 wk later	Yes	Indurated, fluctuant, may fistulize	Unilateral, one-third bilateral	Common
Granuloma inguinale	Variable	—	Suppurating pseudobubo	10%	1–5%

Reprinted with permission from Stoller JK, Ahmad M, Longworth DL. *The Cleveland Clinic Intensive Review of Internal Medicine.* 3rd ed. Lippincott Williams & Wilkins; 2002:168. Table 14.3.

Quick HIT

Recurrences of HSV

- Recurrences are associated with the following: stress, fever, infection, and sun exposure.
- Recurrent episodes tend to become shorter in duration and less frequent over time.

2. HSV-2
   a. Primary infection results in more severe and prolonged symptoms, lasting up to 3 weeks in duration.
   b. Recurrent episodes are milder and of shorter duration, usually resolving within 10 days. There is also a decrease in the frequency of episodes over time.

c. Constitutional symptoms (e.g., fever, headache, malaise) often present in primary infection.
d. HSV-2 presents with painful genital vesicles or pustules (see Figure 10-6). Other findings are tender inguinal lymphadenopathy and vaginal and/or urethral discharge.

3. Disseminated HSV
   a. Usually limited to immunocompromised patients.
   b. May result in encephalitis, meningitis, keratitis, chorioretinitis, pneumonitis, and esophagitis.
   c. Rarely, pregnant individuals may develop disseminated HSV, which can be fatal to the mother and fetus.

Quick HIT

Herpetic Whitlow

- HSV infection of the finger caused by inoculation into open skin surface. Common in healthcare workers.
- Painful vesicular lesions erupt at the fingertip.
- It may cause fever and axillary lymphadenopathy.
- Treat with acyclovir. Do not mistake for paronychia. Incision and drainage should NOT be done for herpetic whitlow.

4. Neonatal HSV (vertical transmission at time of delivery) is associated with congenital malformations, intrauterine growth restriction (IUGR), chorioamnionitis, and even neonatal death.
5. Ocular disease—either form of herpes simplex can cause keratitis, blepharitis, and keratoconjunctivitis.

C. Diagnosis

1. The diagnosis can be made clinically when characteristic lesions are recognized.
2. If there is uncertainty, perform the following tests to confirm the diagnosis:
   a. HSV DNR PCR—highest yield test.
   b. Culture of HSV is the gold standard of diagnosis, but low yield with recurrent or healing lesions.
   c. Direct fluorescent assay and ELISA.

D. Treatment

1. There is no cure available for either type of herpes simplex. Antiviral treatment provides symptomatic relief and reduces the duration of symptoms (see below), but does not eliminate latent virus.
2. Mucocutaneous disease
   a. Treat with oral acyclovir for 7 to 10 days.
   b. Valacyclovir and famciclovir have better oral bioavailability.
   c. Oral acyclovir may be given as prophylaxis for patients with frequent recurrences.
   d. Foscarnet may be given for resistant disease in immunocompromised patients.
3. Disseminated HSV warrants hospital admission. Treat with parenteral acyclovir.

Quick HIT

Primary syphilis is characterized by a hard chancre (indurated, painless ulcer with clean base).

Syphilis

A. General Characteristics

1. It is caused by *Treponema pallidum* spirochetes and transmitted by **direct sexual contact** with infectious lesions. Transmission can also occur across the placenta.
2. It is a systemic illness with four stages (see below). The late stages can be prevented by early treatment.

Quick HIT

Most common presentations for syphilis include:
- Genital lesion (chancre)
- Inguinal lymphadenopathy
- Maculopapular rash of secondary syphilis

B. Clinical Features

1. Primary stage
   a. **Chancre**—a typically **painless,** crater-like lesion that appears on the genitalia 3 to 4 weeks after exposure (Figure 10-7)
   b. Heals in 3 to 6 weeks, even without therapy
   c. Highly infectious—anyone who touches the lesion can transmit the infection
2. Secondary stage
   a. This may develop 4 to 8 weeks after the chancre has healed. **A maculopapular rash is the most characteristic finding in this stage**
   b. Other possible manifestations: flu-like illness, aseptic meningitis, hepatitis, adenopathy
   c. Patients are contagious during this stage
   d. About one-third of untreated patients with secondary syphilis develop latent syphilis
3. Latent stage
   a. Latent stage is defined as the presence of positive serologic test results in the absence of clinical signs or symptoms. Two-thirds of these patients remain asymptomatic; one-third develop tertiary syphilis
   b. It is called early latent syphilis if serology has been positive for <1 year. During this time, the patient may relapse back to the secondary phase
   c. It is called late latent syphilis if serology has been positive for >1 year. Patients are not contagious during this time and do not have any symptoms of the disease

FIGURE 10-7 **Chancre of primary syphilis.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 19.15.)

4. Tertiary stage
   a. One-third of untreated syphilis patients in the latent phase enter this stage
   b. It occurs years after the development of the primary infection (up to 30 years later)
   c. Major manifestations include cardiovascular syphilis, neurosyphilis, and gummas (subcutaneous granulomas)
   d. Neurosyphilis is characterized by dementia, personality changes, and **tabes dorsalis** (posterior column degeneration)
   e. It is very rare nowadays due to treatment with penicillin

Quick HIT

Diagnosis of syphilis: first obtain VDRL and RPR. If positive, confirm with FTA-ABS.

Quick HIT

RPR or VDRL may be falsely positive in patients with SLE.

C. Diagnosis

1. Dark-field microscopy (definitive diagnostic test)—examines a sample of the chancre with visualization of spirochetes. No longer in widespread clinical use as more convenient tests are now available
2. Serologic tests (most commonly used tests)
   a. Nontreponemal tests—RPR, VDRL (most commonly used)
      - High sensitivity—ideal for screening
      - Specificity is only around 70%. If positive, confirmation is necessary with the specific treponemal tests

   b. Treponemal tests—FTA-ABS, MHA-TP
      - More specific than nontreponemal tests
      - Usually used for confirmation of a positive nontreponemal test and not for screening
3. All patients should be tested for HIV infection

D. Treatment

1. Antibiotics are effective in early syphilis but less so in late syphilis.
2. Benzathine penicillin g (one dose IM) is the preferred agent. If the patient is allergic to penicillin, give oral antibiotics (doxycycline, tetracycline) for 2 weeks.
3. If the patient has late latent syphilis or tertiary syphilis, give penicillin in three doses IM once per week.
4. Repeat nontreponemal tests at 6 and 12 months following treatment to ensure adequate response to treatment. Titers should decrease fourfold within 6 months. If they do not, that may signal treatment failure or reinfection.

Quick HIT

Diagnosis of Chancroid

- Painful genital ulcer(s)
- Tender lymphadenopathy
- Syphilis ruled out (negative serologic tests)
- HSV ruled out based on clinical presentation or negative culture for HSV

Chancroid

- Caused by *Haemophilus ducreyi,* a gram-negative rod.
- Transmission through sexual contact.
- Incubation period of 4 to 10 days
- There are no systemic findings. Disseminated infection does not occur.
- Clinical features: **painful genital ulcer(s)** that can be deep with ragged borders and with a purulent base (Figure 10-8); unilateral tender inguinal lymphadenopathy (“buboes”) that appears 1 to 2 weeks after ulcer.
- Diagnosis is usually made clinically. Rule out syphilis and HSV and consider testing for HIV. No serologic tests are available, and culture of the organism is not practical because it requires special media that are not widely available. NAAT is not widely available.
- Treatment options include azithromycin (oral, one dose), ceftriaxone (IM, one dose), or an oral course of erythromycin or ciprofloxacin.
- With treatment, most ulcers resolve in 1 or 2 weeks.

Lymphogranuloma Venereum

- A sexually transmitted disease **caused by *C. trachomatis.***
- Clinical features—painless ulcer at the site of inoculation that may go unnoticed. A few weeks later, tender inguinal lymphadenopathy (usually unilateral) and constitutional symptoms develop.
- If untreated, proctocolitis may develop with perianal fissures and rectal stricture; obstruction of lymphatics may lead to elephantiasis of genitals.
- Diagnosis is made by *C. trachomatis* NAAT. Serologic testing may also be helpful to support diagnosis.
- The treatment is doxycycline (oral for 21 days).

FIGURE 10-8 **Chancroid.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 19.14.)

Pediculosis Pubis (Pubic Lice)

- Pediculosis pubis (pubic lice or "crabs") is a common STI caused by *Phthirus pubis* (the pubic or crab louse).

- It can be transmitted through sexual contact or fomites (clothing, bedding, towels).
- **Severe pruritus** in the genital region is characteristic. Other hairy areas of the body can be involved.
- Diagnosis is made by examination of hair under microscope (or possibly with the naked eye)—identification of adult lice or nits.
- Treat with topical permethrin or pyrethrins—apply to all hairy regions from neck down and wash off after 10 minutes. Sexual partner(s) should also be treated. Combs, clothes, and bed linens should be washed thoroughly. More than one application may be needed to eradicate infection.

Quick HIT

There are three forms of pediculosis: pediculosis capitis (head lice), pediculosis corpora (body lice), and pediculosis pubis (pubic lice or "crabs").

Skin and Soft Tissue Infections (SSTIs)

Cellulitis

A. General Characteristics

1. Cellulitis is an inflammatory condition of **skin and subcutaneous tissue.** Can be purulent or nonpurulent. Purulent SSTI is usually associated with skin or soft tissue abscess (collection of pus within the dermis or subcutaneous space).
2. It is caused by a wide variety of bacteria, the most common being group A streptococci or *S. aureus.* Skin abscesses are most commonly caused by *S. aureus*.
3. **Likely bacterial pathogens are based on patient histories.** Bacteria gain entry through breaks in the skin: abrasion, IV catheters, incisions, immersion in water, and bites or wounds. Venous stasis diseases, lymphedema, and diabetic ulcers also are associated with cellulitis (see Table 10-7).

4. If untreated, cellulitis may lead to potentially life-threatening bacteremia.

Quick HIT

Patients with cellulitis are predisposed to recurrences in the same area because of damage that occurs to the local lymphatic vessels.

B. Clinical Features

1. Classic findings of skin inflammation: erythema, warmth, pain, swelling (usually unilateral)
2. Fever (may or may not be present)

TABLE 10-7 Common Pathogens in Cellulitis

Means of Bacterial Invasion	Likely Pathogen
Local trauma, breaks in skin	Group A Streptococcus *(S. pyogenes)*
Wounds, abscesses	*S. aureus*
Immersion in water	*P. aeruginosa, Aeromonas hydrophila, Vibrio vulnificus*
Acute sinusitis	*H. influenzae*

Quick HIT

Spread to the face is a worrisome complication of cellulitis, and any evidence of orbital involvement is a medical emergency requiring urgent evaluation by an ophthalmologist.

C. Diagnosis

1. The diagnosis is essentially clinical.
2. Obtain blood cultures if the patient has a fever.
3. Obtain tissue cultures if there is a wound, ulcer, or abscess with severe local infection. Routine skin cultures are not useful in guiding treatment, as they rarely identify the causative organism.

4. Obtain imaging (plain film, CT, or MRI) if there is suspicion of deeper infection.

D. Treatment

1. Base treatment on suspected pathogens from the patient history. Patients with systemic signs of infection or rapid progression of erythema require parenteral antibiotics. Those with mild infection can be treated with oral antibiotics.
2. Treatment should cover group A streptococci and MSSA (e.g., oxacillin, cefazolin, cephalexin). If purulent infection or signs of systemic toxicity, cover for MRSA (e.g., vancomycin, TMP-SMX, doxycycline).
3. Continue antibiotics until signs of infection improve. If on parenteral antibiotics, in general, can deescalate to oral antibiotics after 24 to 48 hours of clinical improvement. General duration ranges from 5 days (usually sufficient) to up to 14 days if slow to respond.
4. If there is a drainable abscess, incision and drainage should be done.

Erysipelas

- Erysipelas is a cellulitis that is usually confined to the dermis and lymphatics (see also Clinical Pearl 10-5).
- It is usually caused by group A streptococci (other forms of streptococci less commonly).
- The classic presentation is a well-demarcated, fiery red, painful lesion, most commonly on the lower extremities and the face (Figure 10-9). High fever and chills may be present.
- Predisposing factors include lymphatic obstruction (e.g., after radical mastectomy), local trauma or abscess, fungal infections, diabetes mellitus, and alcohol use disorder.
- Complications include sepsis, local spread to subcutaneous tissues, and necrotizing fasciitis.
- Treatment for uncomplicated cases is oral penicillin or amoxicillin; otherwise treat as for cellulitis. Has a high rate of recurrence.

CLINICAL PEARL 10-5

Differentiating Deep Vein Thrombosis (DVT) From Cellulitis

- Like cellulitis, acute DVT also presents with erythema, warmth, and tenderness in the affected extremity.
- Homans sign and the palpation of venous cords are not sensitive in detecting DVT. Wells score can overestimate probability of DVT in patients with lower extremity cellulitis.
- If cellulitis is suspected based on history and physical, treat empirically and observe for response. Perform venous Doppler if does not respond to treatment of cellulitis or if there are other risk factors for DVT (e.g., prolonged immobility, active cancer, recent trauma or surgery). Do not routinely perform venous Doppler in all patients with lower extremity cellulitis.

FIGURE 10-9 **Erysipelas of the face with characteristic clear delineation between involved and uninvolved skin.** (Reprinted with permission from Werner R. *A Massage Therapist's Guide to Pathology*. 5th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012. Figure 2.23.)

Necrotizing Fasciitis

- Necrotizing fasciitis is a life-threatening infection of deep soft tissues that rapidly tracks along fascial planes.
- Common bacterial causes include *Streptococcus pyogenes, Bacteroides, Clostridium perfringens*, and Enterobacteriaceae. Can be polymicrobial.
- Risk factors include recent surgery, trauma, immunosuppression (diabetes, cirrhosis, HIV, etc.), and IV drug use.
- Clinical features may include fever and pain out of proportion to appearance of skin in early stages, so a high index of suspicion is important. Extension of infection leads to thrombosis of microcirculation, resulting in tissue necrosis, discoloration, crepitus, and cutaneous anesthesia.
- It may rapidly progress to sepsis, toxic shock syndrome (TSS), and multiorgan failure.
- Antibacterial treatment alone is not sufficient. **Rapid surgical exploration and debridement is always indicated (for diagnosis and treatment)!**
- Broad-spectrum parenteral antimicrobial therapy is warranted. Select agent with activity against MRSA (e.g., vancomycin) and broad gram-negative coverage (e.g., carbapenem or piperacillin-tazobactam) in combination with clindamycin for antitoxin effects.

Lymphadenitis or Lymphangitis

- Lymphadenitis is inflammation of a lymph node (single or multiple) usually caused by local skin or soft tissue bacterial infection (often hemolytic streptococci and staphylococci). When inflammation includes the lymphatic channels, it is called lymphangitis.
- It presents with fever, tender lymphadenopathy of regional lymph nodes, and red streaking of skin from the wound or area of cellulitis.
- Complications include thrombosis of adjacent veins, sepsis, and even death if untreated.
- Helpful diagnostic studies include blood and wound cultures.
- Common causative organisms are *S. aureus* and *S. pyogenes*.
- It usually responds well to treatment. Treat with appropriate antibiotics (penicillin G, antistaphylococcal penicillin, or cephalosporin) and warm

compresses. Wound drainage may ultimately be necessary.

Tetanus

A. General Characteristics

1. Causes
   a. It is caused by neurotoxins produced by spores of *Clostridium tetani,* a gram-positive anaerobic bacillus widely found in soil.
   b. *C. tetani* proliferates and produces its **exotoxin** in contaminated wounds. The exotoxin blocks inhibitory transmitters at the neuromuscular junction.
2. Patients at risk are those who have incomplete or no tetanus immunization (see Chapter 12).

TABLE 10-8 Guide to Tetanus Immunization in Wound Management

	Clean, Minor Wounds		Other Wounds	
History of Immunization (Td Doses)	**Td**	**TIG**	**Td**	**TIG**
≥3 known Td doses	No, unless last dose ≥10 years ago	No	No, unless last dose ≥5 years ago	No
<3 doses, unknown status, or >10 yrs since last booster	Yes	No	Yes	Yes

Td, tetanus/diphtheria toxoid; TIG, tetanus immune globulin.

Quick HIT

The following types of wounds are most likely to result in tetanus:

- Wounds contaminated with dirt, feces, or saliva
- Wounds with necrotic tissue
- Deep puncture wounds

B. Clinical Features

1. The classic and earliest symptom is hypertonicity and contractions of the masseter muscles, resulting in *trismus,* or "lockjaw."
2. Progresses to severe, generalized muscle contractions including:
   a. *Risus sardonicus*—grin due to contraction of facial muscles.
   b. *Opisthotonos*—arched back due to contraction of back muscles.
3. Sympathetic hyperactivity.

Quick HIT

The incubation period for tetanus ranges from about 2 days to 2 weeks. The onset of symptoms is characteristically gradual (1 to 7 days).

C. Diagnosis

1. The diagnosis is mainly clinical.
2. Obtain wound cultures, but they are not a reliable means of diagnosis.

D. Treatment

1. Admit the patient to the ICU and provide respiratory support if necessary (see also Table 10-8). Give benzodiazepines for tetany.
2. Neutralize unbound toxin with passive immunization—give a single IM dose of tetanus immune globulin (TIG).
3. Provide active immunization with tetanus/diphtheria toxoid (Td).
4. Thoroughly clean and debride any wounds with tissue necrosis.
5. Give antibiotics (metronidazole or penicillin G), although efficacy is somewhat controversial.

Quick HIT

Common Bugs in Osteomyelitis

- Catheter-associated bacteremia: *S. aureus*
- Orthopedic hardware/prosthetic joint: coagulase-negative staphylococci
- Diabetic foot ulcer: polymicrobial organisms
- Nosocomial infections: *Pseudomonas* spp.
- IV drug use, neutropenia: fungal species, *Pseudomonas* spp.
- Sickle cell disease: *Salmonella* spp.

Infections of the Bones and Joints

Osteomyelitis

A. General Characteristics

1. Osteomyelitis refers to inflammatory destruction of bone due to infection.
2. There are two main categories of osteomyelitis.
   a. Hematogenous osteomyelitis (most common in children)—occurs secondary to bacteremia.
   b. Direct spread of bacteria from any of the following:
      - An adjacent infection (e.g., infected diabetic foot ulcer, decubitus ulcer).
      - Trauma (e.g., **open fractures**).
      - Vascular insufficiency (e.g., peripheral vascular disease).
3. The most common microorganisms causing osteomyelitis are *S. aureus* and coagulase-negative staphylococci.
4. Osteomyelitis can involve any bone. Common locations include long bones (tibia, humerus, femur), foot and ankle, and vertebral bodies.

B. Risk Factors (for complications or chronic osteomyelitis)

1. Open fractures

2. Diabetes mellitus (causes predisposition to infection and peripheral vascular disease)
3. Use of injection drugs
4. Bacteremia, especially endocarditis
5. Presence of indwelling intravascular devices or orthopedic hardware
6. Hemodialysis
7. Sickle cell disease

Quick HIT

Up to 10% of patients with open fractures eventually develop osteomyelitis. Use of orthopedic hardware increases this risk (foreign body is the site of bacterial colonization).

C. Clinical Features

1. Dull pain over the involved area of bone is the most common finding.
2. Localized erythema, warmth, or swelling may be present.
3. Systemic symptoms (e.g., fever, headache, fatigue) may be present, but are inconsistent findings.
4. A draining sinus tract through the skin may form in chronic disease.

Quick HIT

Osteomyelitis of the vertebral body due to *M. tuberculosis* is called **Pott disease.**

D. Diagnosis

1. While bone biopsy is the most accurate method to confirm osteomyelitis, this diagnosis is often made based on clinical picture with supporting evidence of radiographic findings, blood cultures, and inflammatory markers
2. WBC count—may or may not be elevated and is not useful for diagnosis
3. ESR and CRP

a. These are fairly nonspecific, but if these markers of inflammation are elevated in the appropriate clinical setting, consider a diagnosis of osteomyelitis. However, a normal ESR and CRP do not exclude the diagnosis
b. **Both ESR and CRP are very useful in monitoring the response to therapy**
4. **Needle aspiration** of infected bone or bone biopsy (obtained in operating room)—**most direct and accurate means of diagnosis.** Culture results can determine the specific antibiotic therapy
5. Plain radiography
   a. The earliest radiographic changes (periosteal thickening or elevation) are not evident for at least 14 days, so most useful when symptoms have persisted for ≥2 weeks
   b. Lytic lesions are only apparent in advanced disease
6. **MRI is generally the most effective imaging study for diagnosing osteomyelitis and assessing the extent of disease process**
7. Radionucleotide bone scans—usually positive within 2 to 3 days of infection, but are relatively nonspecific (can be positive in metastatic bone disease, trauma, or overlying soft tissue inflammation), so are not often done

E. Treatment

Give IV antibiotics for extended periods (4 to 6 weeks). Whenever possible, initiate antibiotic therapy only after bone cultures are obtained, unless the patient is hemodynamically unstable. General guidelines:

1. Empiric therapy depends on suspected causative organism and requires antibiotics with high bone penetration.
2. If a gram-negative organism is suspected, antibiotic choices include cephalosporins (ceftriaxone, cefuroxime), fluoroquinolones (levofloxacin, ciprofloxacin, moxifloxacin), and carbapenems.
3. If a gram-positive organism is suspected, choose an antibiotic with activity against MRSA such as vancomycin, linezolid, daptomycin, and clindamycin. If other gram-positive organism (not MRSA), can treat with oxacillin, ampicillin, or cefazolin. Rifampin can also be added as adjunct to help with biofilm penetration.

4. Surgical debridement of infected necrotic bone is an important aspect of treatment.

Quick HIT

Chronic osteomyelitis refers to bone necrosis and soft tissue compromise or to a relapse of previously treated osteomyelitis. It is very challenging to treat and almost impossible to completely eradicate.

Acute Infectious Arthritis

A. General Characteristics

1. Acute infectious arthritis occurs when microorganisms (usually bacteria) invade the joint space (not the bone itself), where they release endotoxins and trigger cytokine release and neutrophil infiltration. These inflammatory reactions ultimately lead to erosion and destruction of the joint

CLINICAL PEARL 10-6

Gonococcal Arthritis

- This presents with acute monoarthritis or oligoarthritis, and often progresses within days in a migratory or additive pattern.
- Knees, wrists, hands, and ankles are the most commonly involved.
- Tenosynovitis is often present in the hands and feet.
- Fever, chills, and rash (macules, papules, and/or pustules) are signs of disseminated gonococcal infection. If the patient has disseminated gonococcal infection, admit to the hospital.
- After the joint is initially aspirated, repeated aspiration is unnecessary (unlike in other causes of septic arthritis), and antibiotics alone usually lead to improvement. Treat presumptively for chlamydial infection (e.g., with doxycycline).
- Test for HIV and syphilis. Educate the patient about safe sex practices.

Quick HIT

If patient has a painless range of motion of involved joint, septic arthritis is very unlikely, even in the presence of erythema. Micromotion of joint causes severe pain in septic arthritis.

2. Pathogenesis—microorganisms penetrate the joint via the following mechanisms:
   a. Hematogenous spread—most common route
   b. Contiguous spread from another locus of infection (e.g., osteomyelitis, abscess, or cellulitis).
   c. Traumatic injury to joint
   d. Iatrogenic (e.g., from arthrocentesis, arthroscopy)
3. Microbiology
   a. Most infections are monomicrobial (due to one bacteria)
   b. Acute bacterial arthritis can be caused by any of the following:
      - ***S. aureus*** **is the most common agent overall in adults and children.** Various streptococcal species are also frequently involved.
      - An important gram-negative agent is *N. gonorrhoeae.* **Gonococcal arthritis is the most common cause of acute infectious arthritis in young, sexually active adults (see also** Clinical Pearl 10-6).
      - Consider gram-negative organisms such as *Pseudomonas aeruginosa* or *Salmonella* spp. if there is a history of sickle cell disease, immunosuppression, or IV drug use.
4. Other risk factors for acute infectious arthritis.
   a. Prior joint damage (e.g., rheumatoid arthritis)
   b. Joint prosthesis or recent joint injection
   c. Immunosuppression (including diabetes)
   d. Overlying skin and soft tissue infection

Quick HIT

Septic Arthritis

- **The most common joint affected is the knee.** The hip, wrist, shoulder, and ankle may also be involved.
- Patients with immunosuppression or connective tissue diseases may have polyarticular arthritis (and a worse prognosis).

B. Clinical Features

1. The joint is swollen, warm, and painful.
   a. **The range of motion (active or passive) is very limited.**
   b. An effusion can be palpated.
2. Constitutional symptoms such as fever, chills, and malaise are common.

C. Diagnosis

1. Perform a joint aspiration ("tap") and analysis of synovial fluid in all patients suspected of having a septic joint. Order the following studies on aspirated synovial fluid
   a. WBC count with differential—usually >50,000 WBCs/mm^3 with >80% PMNs—the most helpful test
   b. Gram stain of fluid—positive in approximately 75% of gram-positive cases, but only 30% to 50% of gram-negative cases
   c. Culture—aerobic and anaerobic
   d. Crystal analysis—keep in mind that acute gout may present like septic arthritis
   e. NAAT or PCR of synovial fluid—this may be useful if gonococcal arthritis is suspected but Gram stain and cultures are negative
2. Blood cultures are positive in approximately 50% of all cases (frequently negative in gonococcal arthritis)

TABLE 10-9 Medical Treatment of Acute Bacterial Arthritis

Adult (Relatively Healthy): Treat for *S. aureus*	Patient is Immunocompromised or Has Significant Risk Factors for Gram-Negative Arthritis	Young Adult With History and Presentation Consistent With Gonococcal Arthritis
Parenteral, β-lactamase–resistant penicillin (e.g., oxacillin) or first-generation cephalosporin	Parenteral, broad-spectrum antibiotics (with gram-negative coverage) (e.g., a third-generation cephalosporin or aminoglycoside)	Parenteral, third-generation cephalosporin (e.g., ceftriaxone) until there is improvement
Treat with vancomycin if MRSA is suspected	For pseudomonal infection, use fluoroquinoone, cephalosporin with anti-pseudomonal activity, carbapenem, or aminoglycoside	Switch to an oral agent with gram-negative coverage (e.g., ciprofloxacin) once there is clinical improvement

3. Other laboratory abnormalities
   a. Leukocytosis—present in about half of patients with a septic joint.
   b. Elevated ESR and CRP (inflammatory markers)—usually elevated, and helpful in monitoring response to clinical treatment
4. Imaging studies.
   a. Plain radiographs—generally not useful to make diagnosis of septic arthritis unless joint damage is severe, but can be helpful to evaluate for coexisting bone and joint disease
   b. CT or MRI—helpful if the sacroiliac or facet joints are involved (difficult joints to examine otherwise)
5. Obtain cultures from appropriate mucosal surfaces (e.g., genitourinary tract) if gonococcal arthritis is suspected

D. Treatment

1. Prompt antibiotic treatment.
   a. Do not delay in initiating antimicrobial therapy when acute infectious arthritis is suspected.
   b. If the Gram stain result is negative but acute bacterial arthritis is still suspected, treat empirically based on the clinical scenario (see Table

10-9) until culture and sensitivity results are available.

c. Duration of therapy varies depending on organism, surgical treatment, and concomitant disorder (e.g., endocarditis and bacteremia warrant longer treatment courses). Usually at least 14 days and up to 3 to 4 weeks in some cases.

2. Drainage

a. Daily aspiration of affected joint as long as effusion persists is one treatment option. However, surgical washout is recommended to prevent further damage to the articular cartilage that occurs with persistent infectious process. Certain joints are amenable to arthroscopic drainage (shoulder, knee) whereas others are not (hip, wrist, elbow, ankle) and should be opened.

Quick HIT

Complications of Septic Arthritis

- Destruction of joint and surrounding structures (e.g., ligaments, tendons), leading to stiffness, pain, and loss of function
- Avascular necrosis (if hip is involved)
- Sepsis

Quick HIT

Lyme disease is the most common vector-borne illness in the United States. The peak incidence is in summer months. It is associated with outdoor activities in wooded areas (e.g., hiking, camping).

Zoonoses and Arthropod-Borne Diseases

Lyme Disease

A. General Characteristics

1. Three major endemic areas in the United States (although incidence of Lyme disease in the U.S. is steadily increasing and expanding to other areas)
   a. Northeastern seaboard (from Maine to Maryland)
   b. Midwest (north central states—e.g., Minnesota, Wisconsin)
   c. West coast (Northern California)
2. Incubation period is 3 to 32 days
3. Transmission cycle
   a. Caused by spirochete *Borrelia burgdorferi*
   b. Transmitted by ticks—commonly the deer tick *Ixodidae scapularis*
   c. The tick is hosted by white-footed mice (immature ticks), white-tailed deer (mature ticks), and brief encounters with humans

FIGURE 10-10 **Erythema migrans (Lyme disease).**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 7.19.)

Quick **HIT**

- Patients with tick bites should be followed up closely for the appearance of erythema migrans, but the majority of tick bites do not result in infection.
- A vaccine against *B. burgdorferi* has been developed but was taken off the market due to lack of use in the medical community.

B. Clinical Features

1. Stage 1—early, localized infection
   a. **Erythema migrans** is the hallmark skin lesion at site of the tick bite. Characteristically it is a large, painless, well-demarcated target-shaped lesion, commonly seen on the thigh, groin, or axilla (Figure 10-10)

   b. Multiple lesions signify that hematogenous spread has occurred (see below)
2. Stage 2—early, disseminated infection
   a. Infection spreads via lymphatics and the bloodstream within weeks to months after initial tick bite
   b. Clinical features: intermittent flu-like symptoms, headaches, neck stiffness, fever/chills, fatigue, malaise, musculoskeletal pain
   c. After several weeks, about 15% of patients develop one or several of the following (usually resolve within several months):
      - Meningitis
      - Encephalitis (rare)
      - Unilateral or bilateral cranial nerve palsy (especially facial nerve)
      - Peripheral radiculoneuropathy (motor or sensory)
      - Mononeuropathy multiplex
   d. About 1% will have cardiac manifestations (e.g., AV block, pericarditis, carditis). These usually only last for several weeks, but recurrence is common
3. Stage 3—late, persistent infection (months to years after initial infection, may not be preceded by early disseminated disease)
   a. Arthritis—This occurs in 60% of untreated patients; it typically affects the large joints (especially knees). Chronic arthritis will develop in some patients
   b. Chronic CNS disease—subacute, subtle encephalitis, transverse myelitis, or axonal polyneuropathy
   c. Acrodermatitis chronica atrophicans (a rare skin lesion)—reddish-purple plaques and nodules on the extensor surfaces of the legs

C. Diagnosis

1. Method of diagnosis depends on stage of disease
2. Early, localized disease—diagnosis can be made clinically based on erythema migrans in a patient with a history of tick exposure in an endemic area without need for laboratory confirmation. Treat empirically

CLINICAL PEARL 10-7

Lyme Serology

- IgM antibodies peak 3 to 6 weeks after the onset of symptoms. If a few months have passed since the onset of disease, IgM levels are basically worthless.
- IgG antibodies slowly increase and remain elevated in patients with disseminated illness. If a patient has had Lyme disease in the past and now has symptoms consistent with new illness, IgG levels will not indicate whether the infection is acute or chronic.
- Patients with a history of distant Lyme disease may have elevated IgG levels despite adequate antibiotic treatment.
- IgG antibodies cross-react with *T. pallidum*, but patients with Lyme disease will not have a positive VDRL.

Quick HIT

Early treatment with antibiotics is extremely important because later sequelae of disease can usually be prevented. Treatment in later stages is usually effective, but recovery may be delayed.

3. Early disseminated or late Lyme disease—serologic studies are important to confirm diagnosis (see also Clinical Pearl 10-7)
   a. ELISA is used to detect serum IgM and IgG antibodies during the first month of illness
   b. Western blot is used to confirm positive or equivocal results

D. Treatment

1. Early localized disease
   a. If it is confined to the skin, 10 days of doxycycline is adequate
   b. If there is any evidence of early disseminated disease, extend treatment to 14 to 21 days
   c. For early Lyme disease
      - Oral doxycycline (for 21 days)—relatively contraindicated in pregnant women and in children <8 years of age
      - Amoxicillin, cefuroxime, and clarithromycin are alternative agents

2. Treatment of complications such as facial nerve palsy, arthritis, or cardiac disease is prolonged antibiotic therapy (14 to 28 days). For meningitis or other CNS complications, treat with IV antibiotics for 14 to 21 days

Rocky Mountain Spotted Fever (RMSF)

A. General Characteristics

1. Caused by the intracellular, gram-negative bacteria *Rickettsia rickettsii.*
2. Ticks feeding on various mammals serve as vectors for disease transmission.
3. The major endemic areas include the southeastern, south-central, midwestern, and western United States. Peak incidence is in the spring and summer months due to increased outdoor activity.
4. Pathophysiology of disease.
   a. Organisms enter the host cells via tick bites, multiply in the vascular endothelium, and spread to different layers of the vasculature.
   b. Damage to the vascular endothelium results in increased vascular permeability, activation of complement, microhemorrhages, and microinfarcts.

B. Clinical Features

1. The onset of symptoms is typically 5 to 7 days after the tick bite, although incubation can be as long as 14 days.
2. It classically presents with fever, chills, malaise, nausea, vomiting, myalgias, photophobia, and headache.
3. A blanching erythematous rash usually appears after 4 to 5 days of fever. **Rash starts peripherally (wrists, forearms, palms, ankles, and soles) but then spreads centrally** (to the rest of the limbs, trunk, and face). It becomes maculopapular, and eventually petechial.
4. It may lead to encephalitis, interstitial pneumonitis, cardiac arrhythmias, GI bleeding, and coagulopathy.

C. Diagnosis

1. Diagnosis is primarily clinical. Laboratory abnormalities may include elevated liver enzymes and thrombocytopenia.
2. Acute and convalescent serology and immunofluorescent staining of skin biopsy are confirmatory tests. In some labs, PCR testing for RMSF may be available. *R. rickettsia* cannot be cultured easily in most labs.

D. Treatment

1. Doxycycline—usually given for 7 days; given intravenously if the patient is vomiting. This is preferred even in pregnancy (teratogenic effects are extremely rare and alternative agents are less effective).
2. Alternative agent—give chloramphenicol for those with history of severe adverse reaction with doxycycline.

Malaria

A. General Characteristics

1. A protozoal infection caused by one of four organisms
   a. *Plasmodium falciparum*
   b. *Plasmodium ovale*
   c. *Plasmodium vivax*
   d. *Plasmodium malariae*
2. Prevalent in tropical climates, parts of Africa, Southeast Asia, and the Middle East
3. Transmitted via *Anopheles* spp. mosquito bite in endemic areas

Quick HIT

The onset of illness in malaria usually occurs weeks to months after infection, but it is dependent on the specific cause.

B. Clinical Features

1. Symptoms may include fever and chills, myalgias, headache, nausea, vomiting, and diarrhea

2. Fever pattern varies depending on cause
   a. *P. falciparum, P. ovale*, and *P. vivax*—fever usually spikes every 48 hours
   b. *P. malariae*—fever usually spikes every 72 hours

Quick HIT

P. falciparum infection is by far the most serious and life-threatening cause of malaria.

C. Diagnosis

1. Identify organism on peripheral blood smear
2. Blood smear must have **Giemsa stain**

Quick HIT

Side effects of medications can be a factor in choosing appropriate malaria prophylaxis:

- Atovaquone–proguanil is contraindicated in patients with advanced renal failure and pregnancy.
- Mefloquine is contraindicated in patients with seizures and major psychiatric disorders.
- Chloroquine is well tolerated and can be used in pregnancy.
- Primaquine is contraindicated in patients with G6PD deficiency due to precipitation of hemolytic anemia.

D. Treatment

1. Use chloroquine phosphate unless resistance is suspected. In many countries, chloroquine resistance is so prevalent that it should be assumed.
2. If chloroquine resistance is suspected, give combination therapy. Choices include artemisinin-based combinations (e.g., artemether-lumefantrine, artesunate-mefloquine), or non–artemisinin-based combinations such as atovaquone-proguanil or quinine plus doxycycline.
3. *P. falciparum* infection may require IV quinidine and doxycycline.

4. Relapses can occur in *P. vivax* and *P. ovale* infection as a result of dormant hypnozoites in the liver. Add a 2-week regimen of primaquine phosphate for these types of malarial infection.
5. Prophylaxis is important for travelers to endemic regions. Mefloquine is the agent of choice in chloroquine-resistant areas. Chloroquine can be used in areas where chloroquine resistance has not been reported.

Rabies

A. General Characteristics

1. A devastating, deadly viral encephalitis
2. Contracted from a bite or scratch by an infected animal (dog, bat, raccoon, fox, coyote); infection from a corneal transplant has been documented as well
3. More prevalent in developing countries where rabies vaccination of animals is not widespread

B. Clinical Features

1. The incubation period typically ranges from 30 to 90 days, but varies considerably.
2. Once symptoms are present, rabies is almost invariably fatal
3. Symptoms (in progressive order)
   a. Pain at site of bite
   b. Prodromal symptoms of sore throat, fatigue, headache, nausea, and/or vomiting
   c. Encephalitis—confusion, combativeness, hyperactivity, fever, and seizures may be present
   d. Hydrophobia—inability to drink due to laryngeal spasm, hypersalivation (“foaming at mouth”), usually progresses to coma and death
   e. Some patients may present with ascending paralysis

Quick HIT

Pre-exposure prophylaxis—Rabies vaccine is available for at-risk individuals (e.g., those with potential occupational exposure, such as veterinarians, wildlife officials, and laboratory workers).

C. Diagnosis

1. Clinically diagnosed based on a thorough history, as antibodies may not be present until late disease. Consider this diagnosis for any patient with acute progressive encephalitis.
2. Virus PCR or viral antigen can be identified in infected tissue. Virus can be isolated in saliva as well.
3. Fourfold increase in serum antibody titers.
4. Histologic identification of **Negri bodies** (eosinophilic intracytoplasmic inclusion bodies), mostly useful for postmortem testing.

D. Treatment (Postexposure Management)

1. Clean the wound thoroughly with soap and water. Use povidone-iodine if available and offer tetanus vaccination.
2. For wild animal bites (e.g., bat or raccoon), the animal should be captured if possible, destroyed, and sent to a laboratory for immunofluorescence of brain tissue.
3. If a patient was bitten by a healthy dog or cat in an endemic area, the animal should be captured and observed for 10 days. If there is no change in the animal's condition, then it most likely does not have rabies.
4. For known rabies exposure, both of the following should be performed.
   a. Passive immunization—administer the human rabies immunoglobulin to patients, into the wound as well in the gluteal region.
   b. Active immunization—administer the antirabies vaccine in three IM doses into the deltoid or thigh over a 14-day period.

Other Zoonoses

- Table 10-10 covers leptospirosis, ehrlichiosis, tularemia, Q fever, and cat scratch fever.

Common Fungal Infections

Candidiasis

A. General Characteristics

1. *Candida* species are oval, budding yeasts known for their formation of hyphae and long pseudohyphae. They normally colonize humans, and the overgrowth of these organisms results in the clinical pathology of candidiasis
2. *Candida albicans* is the most common cause of candidiasis
3. Risk factors for candidiasis
   a. Antibiotic therapy
   b. Diabetes mellitus
   c. Immunocompromised hosts (increased risk for both mucocutaneous and systemic candidiasis)

B. Clinical Features

1. Typical presentation is local mucocutaneous infection. The most common affected areas are:
   a. Vulvovaginitis—"yeast infection"
      - This results in a thick, white, "cottage cheese-like" vaginal discharge
      - The discharge characteristically is painless but does cause pruritus
   b. Oropharyngeal candidiasis—"thrush"
      - This causes thick, white, scrapable plaques that adhere to the oral mucosa (Figure 10-11)
      - Usually painless but those with dentures may have stomatitis
      - Unexplained oral thrush should raise suspicion of cellular immunodeficiency such as HIV infection

c. Cutaneous candidiasis

- This causes erythematous, eroded patches with “satellite lesions” (Figure 10-12)
- It is more common in obese diabetic patients; it appears in skin folds (e.g., axilla, groin, underneath breasts) and in macerated skin areas

d. Esophagitis

- Candida esophagitis may cause significant odynophagia
- Most common in HIV-infected patients and diagnosed by endoscopy

2. Disseminated or invasive disease may occur in immunocompromised hosts. Manifestations include sepsis/septic shock, meningitis, and multiple abscesses in various organs

TABLE 10-10 Other Zoonoses and Arthropod-Borne Diseases

Disease	Organism	Transmission	Reservoir	Clinical Findings	Diagnosis	Treatment
Leptospirosis	*Leptospira* spp. (spirochetes)	Contaminated water	Rodents, farm animals	Fever, headache, conjunctival suffusion, rash, LAD,[a] ↑ AST and ALT. When severe, renal failure, jaundice, meningitis	PCR, serology ELISA, or blood or urine cx[a]	Oral antibiotics: doxycycline; if severe, IV penicillin G
Ehrlichiosis	*Ehrlichia* spp. (intracellular, gram-negative bacteria)	Tick bite	Deer	Fever, chills, malaise ± rash **Complications:** renal failure, GI bleeding	Clinical; confirm with PCR or serology	Oral doxycycline × 7–10 days
Tularemia	*Francisella tularensis* (small gram-negative bacillus)	Tick bite, animal bites, handling carcass	Rabbits, other rodents	Fever, headache, nausea; ulcer at site of tick bite; painful LAD	Serology (serial sample to show rise in titer), blood or wound cx but rarely positive	IM streptomycin or gentamicin
Q fever	*C. urnetiid* (gram-negative organism)	Blood, ingestion of infected milk, inhalation	Farm animals	**Acute:** constitutional symptoms, nausea, vomiting **Chronic:** endocarditis	Serology or PCR, organism does not grow on routine blood cx	**Acute:** doxycycline or TMP-SMX **Chronic:** rifampin
Cat scratch disease	*Bartonella henselae* (gram-negative bacillus)	Scratch from a flea-infested cat	Cats, fleas	LAD or lymphadenitis; systemic symptoms rare	Serology, PCR	Usually self-limited; if severe, azithromycin or doxycycline plus rifampin

[a]LAD, lymphadenopathy; cx, culture.

FIGURE 10-11 **Oral candidiasis.**
(Reprinted with permission from Harpavat S, Nissim S. *Lippincott's Microcards: Microbiology Flash Cards*. 3rd ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. Figure 124.1.)

FIGURE
10-12 **Cutaneous candidiasis with characteristic satellite lesions beyond the plaques.**
(Reprinted with permission from Goodheart HP, Gonzalez ME. *Goodheart's Same-Site Differential Diagnosis*. 2nd ed. Wolters Kluwer; 2022. Figure 11.55.)

C. Diagnosis

1. Mucocutaneous candidiasis diagnosis is primarily clinical based on typical appearance of skin or oral lesions; KOH preparation demonstrates yeast.
2. Invasive candidiasis is diagnosed by blood or tissue culture.

D. Treatment

1. Remove indwelling catheters or central lines
2. Acceptable treatments for oropharyngeal candidiasis
   a. Clotrimazole troches (dissolve in the mouth) five times per day
   b. Nystatin mouthwash ("swish and swallow") three to five times per day; only for oral candidiasis
   c. Oral ketoconazole or fluconazole for esophagitis

3. Vaginal candidiasis—miconazole or clotrimazole cream
4. Cutaneous candidiasis—oral nystatin powder, keeping skin dry
5. For systemic candidiasis, use echinocandins (e.g., caspofungin, micafungin, and anidulafungin). Azoles can also be used (e.g., fluconazole, voriconazole, posaconazole). Amphotericin B is reserved for cases when antifungal resistance is suspected due to its high toxicity

Aspergillus

A. General Characteristics

1. *Aspergillus* spp. spores are found everywhere in the environment. Typically, disease occurs when spores are inhaled into the lung.
2. There are three main types of clinical syndromes associated with *Aspergillus* (see clinical features below).
3. Invasive aspergillosis is usually limited to severely immunocompromised patients. It should be considered in any immunocompromised patient with fever and respiratory distress despite use of broad-spectrum antibiotics.

B. Clinical Features

1. Allergic bronchopulmonary aspergillosis
   a. A type I hypersensitivity reaction to *Aspergillus.*
   b. It presents with **asthma and eosinophilia.** Recurrent exacerbations are common.
2. Pulmonary aspergillosis
   a. Pulmonary aspergilloma is a fungus ball caused by inhalation of spores into the lung. Patients with a history of sarcoidosis, histoplasmosis, TB, and bronchiectasis are at risk.
   b. It presents with chronic cough; hemoptysis may be present as well.
   c. It may resolve spontaneously or invade locally.
   d. In immunocompetent hosts, pulmonary aspergillosis can take on several forms, including aspergillus nodules (usually asymptomatic and found incidentally on imaging), chronic cavitary pulmonary aspergillosis, and chronic fibrosing aspergillosis.
3. Invasive aspergillosis

a. This occurs when hyphae invade the lung vasculature, resulting in thrombosis and infarction.
b. Hosts are typically at-risk patients with neutropenia, acute leukemia, transplant recipients, and patients with stage 3 HIV.
c. It usually presents with acute onset of fever, cough, respiratory distress, and diffuse, bilateral pulmonary infiltrates.
d. It is transmitted via hematogenous dissemination, and may invade the sinuses, orbits, and brain.

C. Diagnosis

1. CXR reveals a dense pulmonary consolidation and sometimes a **fungus ball.** CT scan is best for detecting early focal lesions.
2. Definitive diagnosis of invasive aspergillosis is by tissue biopsy, but this is not done often due to risk of complications. Diagnosis is presumed when *Aspergillus* is isolated from the sputum or BAL specimen of a severely immunocompromised/neutropenic patient with clinical symptoms.
3. Other noninvasive testing includes fungal serum biomarkers (e.g., serum galactomannan or β-D-glucan assay, which detects fungal cell wall and is not specific for aspergillus).
4. Blood cultures are usually not helpful because they are rarely positive.

D. Treatment

1. For allergic bronchopulmonary aspergillosis, patients should avoid exposure to *Aspergillus;* corticosteroids may be beneficial.
2. For pulmonary aspergillosis, patients with massive hemoptysis may require surgical resection. Aspergillus nodules can be observed. If patients develop chronic cavitary or fibrosing pulmonary aspergillosis, treat with antifungal therapy.
3. For invasive aspergillosis, treat with IV voriconazole (first line). Alternative therapy includes liposomal amphotericin B, isavuconazole, posaconazole, or combination of voriconazole + echinocandin.
4. Suspicion of head or brain involvement warrants prompt evaluation (imaging studies). For invasive rhinosinusitis, emergent debridement is needed. Surgical debridement is also indicated for any localized cutaneous infections.

Cryptococcosis

A. General Characteristics

1. Caused by *Cryptococcus neoformans,* a budding, round yeast with a thick polysaccharide capsule
2. Classically associated with pigeon droppings, although most patients do not have history of pigeon exposure
3. Most commonly seen in patients with immunocompromising conditions such as AIDS, prolonged glucocorticoids, organ transplantation, cancer, liver disease, or sarcoidosis
4. Infection is due to inhalation of fungus into lungs. Hematogenous spread may involve the brain and meninges

B. Clinical Features

1. CNS disease—meningitis or meningoencephalitis; brain abscess is also possible
   a. CNS disease is a life-threatening condition that requires prompt treatment (see below). It should always be on the differential diagnosis of an HIV-positive patient with a fever and headache. If untreated, it is almost invariably fatal.
   b. Symptoms include insidious onset of fever, headache, irritability, dizziness, confusion, and possibly seizures.
2. Isolated pulmonary infection may also occur.

C. Diagnosis

1. LP is absolutely essential if meningitis is suspected. Patients suspected of having increased intracranial pressure (focal neurologic deficits, known CNS mass lesion, recent seizure, papilledema, etc.) should undergo neuroimaging before LP.
   a. Opening pressure is usually elevated during LP.
   b. Latex agglutination or ELISA can detect cryptococcal antigen in the CSF.
   c. India ink smear shows encapsulated yeasts.
   d. Culture yields cryptococcal colonies in 3 to 7 days.
2. Tissue biopsy is characterized by **lack of inflammatory response.**
3. The organism may also be cultured from urine and blood.

D. Treatment

1. Use amphotericin B with flucytosine for approximately 2 weeks (induction therapy), followed by oral fluconazole for both consolidative and suppressive therapy.
2. The duration of therapy varies depending on follow-up CSF cultures. Prolonged treatment is usually needed (up to 1 year of suppressive therapy).

Other Fungal Infections

- Table 10-11 covers blastomycosis, histoplasmosis, coccidioidomycosis, and sporotrichosis.

A 39-year-old woman complains of fever, cough, and shortness of breath. She is from Missouri and lives on a farm with her wife and two children. She has never smoked and does not drink alcohol or use illicit drugs. Her temperature is 38.2°C, blood pressure is 112/70 mmHg, heart rate is 90 beats per minute, and respiratory rate is 26 breaths per minute. There are scattered wheezes and rales on pulmonary auscultation, and there are tender, erythematous nodules on the anterior portion of her legs bilaterally. A chest x-ray shows pulmonary infiltrates and hilar lymphadenopathy.

What is the most likely diagnosis?

A. Tuberculosis
B. Hypersensitivity pneumonitis
C. Sarcoidosis
D. Histoplasmosis
E. Coccidioidomycosis

- **The answer is D: Histoplasmosis.** Pulmonary histoplasmosis is one manifestation of infection due to *Histoplasma capsulatum,* which primarily affects people in the Ohio and Mississippi River valleys. Pulmonary infection may be subclinical, but can also cause a severe pneumonia with cavitations, pulmonary nodules, and mediastinal and hilar lymphadenopathy. In immunosuppressed patients, the infection can disseminate and cause fever, skin and oral lesions, hepatosplenomegaly, lymphadenopathy, fibrosing mediastinitis, pericarditis, and other findings. This patient has features of pulmonary histoplasmosis and erythema nodosum, which is associated with histoplasmosis. **(A)** Histoplasmosis can mimic TB, especially in the chronic form that manifests as fevers, weight loss, night sweats, and apical infiltrates on chest x-ray. There are no risk factors for TB mentioned in the vignette, and the patient is from an area endemic for histoplasmosis. **(B)** While this diagnosis may be considered given that she lives on a farm (“farmer’s lung”), it is not

diagnosed with a urine antigen test. **(C)** Sarcoidosis also commonly involves the lungs and causes hilar lymphadenopathy, but is not suggested in this case. **(E)** Coccidioidomycosis also causes pulmonary disease, but affects people in the Southwestern U.S.

TABLE 10-11 Other Important Fungal Infections

Infection	Organism	Transmission	Findings	Diagnosis	Treatment
Blastomycosis	*Blastomyces dermatitidis* (dimorphic fungus)	Inhalation of spores from the environment (endemic in Ohio and Mississippi River valleys, Great Lakes)	Disseminated infection → chronic, indolent disease: constitutional symptoms, LAD, pneumonia	Cx from urine, sputum, body fluids	PO itraconazole × 6–12 mo Amphotericin B for meningitis
Histoplasmosis	*H. capsulatum* (dimorphic fungus with septate hyphae)	Exposure to bird/bat droppings (endemic in Ohio and Mississippi River valleys)	Flu-like symptoms, erythema nodosum, hepatosplenomegaly	Demonstration of yeast in body fluids or skin, histoplasma antigen testing	PO itraconazole; amphotericin B for severe infection or ↓ immunocompromised host
Coccidioidomycosis	*Coccidioides immitis* (dimorphic fungus)	Inhalation of spores (endemic in Southwestern U.S.)	Asymptomatic or nonspecific respiratory symptoms Dissemination → joint, vertebra, or meninges	Serologic tests (cocci EIA), culture of organism from body fluid	PO fluconazole or itraconazole × 6 mo, or amphotericin B for severe infection or immunocompromised host
Sporotrichosis	*Sporothrix schenckii* (dimorphic, cigar-shaped yeast)	Invasion of skin by thorn or other plant material (keyword: gardening)	Lymphocutaneous form: hard, subcutaneous nodules → ulcerate and drain Disseminated form (rare): pneumonia, meningitis	Visualization of yeast in tissue or body fluids	Cutaneous: potassium iodide × 1–2 mo or itraconazole × 3–6 mo; for disseminated infection, amphotericin B

LAD, lymphadenopathy; cx, culture; EIA, enzyme-linked immunoassay.

Common Parasitic Infections

- Table 10-12 covers cryptosporidiosis, amebiasis, giardiasis, ascariasis, hookworm, pinworm (enterobiasis), tapeworm, and schistosomiasis.

Quick HIT

Persistence of fever in the ICU, despite antimicrobial therapy, should raise the index of suspicion for:

- Fungal infection
- Antimicrobial resistance
- Infections requiring surgical intervention (e.g., occult abscess, wound necrosis)
- Infection of indwelling devices
- Drug fever

Fever and Sepsis

Fever of Unknown Origin

A. General Characteristics

1. Defining fever of unknown origin (FUO)
   a. Classically defined as having the following necessary criteria:
      - Fever >38.3°C (101°F)
      - Continuing "on several occasions" for at least 3 weeks
      - No diagnosis over this time period despite 1 week of inpatient workup
   b. Because of changes in medical practice, this definition has been altered: Three outpatient visits now substitute for 1 week in the hospital
2. Causes: with development of better imaging and lab testing, the most common cause is idiopathic (previously infection was the most common cause)
   a. Infection
      - TB and other mycobacterial infection
      - Occult abscesses (e.g., hepatic, intra-abdominal, retroperitoneal)
      - Osteomyelitis
      - UTI/complicated UTI
      - Endocarditis (especially culture-negative endocarditis)
      - Sinusitis or dental abscess

- HIV
- Infectious mononucleosis and other viruses
- Malaria and other parasitic infections

b. Occult malignancy, particularly:

- Lymphoma (especially Hodgkin lymphoma)
- Leukemia
- Renal cell carcinoma
- Hepatocellular carcinoma or metastases to liver

c. Inflammatory diseases, particularly:

- SLE
- Still disease
- Polyarteritis nodosa (PAN)
- Giant cell arteritis
- Polymyalgia rheumatica

d. Other causes (in no particular order)

- Granulomatous disease (e.g., sarcoidosis, Crohn disease)
- Drug fevers (e.g., antibiotics, sulfonamides, NSAIDs, barbiturates, quinidine, procainamide, hydralazine, methyldopa)
- Pulmonary embolism
- Hemolytic anemia
- Hyperthyroidism
- Familial Mediterranean fever
- Crystal arthropathies (gout, pseudogout)
- Factitious illnesses (diagnoses of exclusion)

TABLE 10-12 Important Parasitic Infections

Infection	Organism	Transmission/ Life Cycle	Findings	Diagnosis	Treatment
Cryptosporidiosis	*Cryptosporidium* spp. (spore-forming protozoa)	Fecal–oral route	Watery diarrhea ↓ Severe diarrhea in an immunocompromised host	Stool PCR or microscopy (see oocytes)	Supportive care
Amebiasis	*Entamoeba histolytica* (protozoan)	Fecal–oral route Contaminated water/ food, anal–oral sexual contact	Bloody diarrhea, tenesmus, abdominal pain ± liver abscess	Stool PCR, antigen, or microscopy (see trophozoites)	Metronidazole
Giardiasis	*Giardia lamblia* (protozoan)	Fecal–oral route (as in amebiasis) Hints: daycare, camping	Watery diarrhea Chronic infection; weight loss	Stool antigen or PCR, or microscopy (see cysts or trophozoites)	Tinidazole, nitazoxanide, or metronidazole
Ascariasis	*Ascaris lumbricoides* (roundworms = nematodes)	Ingestion of food or water contaminated by human feces	Varies: no symptoms, postprandial abdominal pain, or vomiting Heavy worm burden: bowel, pancreatic duct or common bile duct obstruction	Stool sample: see eggs or adult worms	Albendazole, mebendazole, or pyrantel pamoate
Hookworm	*Ancylostoma duodenale* or *Necator americanus* (roundworm)	Larvae invade skin → travel to lung → coughed and swallowed → reside in intestine	Usually no symptoms Cough, anemia, malabsorption, weight loss, eosinophilia	Stool sample: see adult worms or eggs	Albendazole, mebendazole, or pyrantel pamoate
Enterobiasis (pinworm)	*Enterobius vermicularis* (roundworm)	Fecal–oral route (self-infection with anus–hand–mouth contact) Common in children	Perianal pruritus, worse at night	"Tape test": see eggs on tape after it is placed near the anus	Albendazole, mebendazole, or pyrantel pamoate
Tapeworm (cestodes)	*Taenia saginata* (beef), *Taenia solium* (pork), *Diphyllobothrium latum* (fish)	Eating raw or undercooked meat	Usually asymptomatic Possible nausea, abdominal pain, weight loss Fish tapeworm: vitamin B_{12} deficiency	Tape test for *D. latum,* stool sample (see eggs)	Praziquantel; vitamin B_{12} if deficient
Schistosomiasis (trematodes)	*Schistosoma mansoni, Schistosoma haematobium, Schistosoma japonicum*	Penetration of human skin (in contaminated fresh water) → migrate to lungs → to portal vein → to venules of mesentery, bladder, or ureters	*S. mansoni* and *S. japonicum:* fever, diarrhea (acute) → liver fibrosis, portal HTN (chronic) *S. haematobium:* urinary tract granulomas → bladder polyps, fibrosis, cancer	Demonstration of eggs in urine or feces, or PCR of serum, feces, or urine	Praziquantel and prednisolone

A 63-year-old man presents to his physician due to persistent fevers. He says that he initially saw a physician for a fever about a month ago, and the workup was negative. He did not receive antibiotics at that time. Since then, he has measured his temperature at home and has had temperatures higher than 38.5°C. He denies any headache, cough, shortness of breath, abdominal pain, jaundice, bone or muscle pain, body swelling, or other concerning symptoms. He is otherwise healthy and sees the physician annually, receiving all necessary screening procedures. He has not traveled recently and has had no sick contacts or animal exposures. On physical examination, a new murmur is heard over the cardiac apex, but the rest of the examination, including assessment of skin and lymph nodes, is unremarkable. Three sets of blood cultures are sent to the laboratory and later return negative. An echocardiogram is performed and shows a vegetation on the mitral valve. Other significant laboratory values include a hemoglobin of 12.4 g/dL, a leukocyte count of 11,500/mm^3, and negative testing for ANA and antiphospholipid antibodies.

Which of the following is the likely cause of this patient's recurring fevers?

A. Malignancy
B. Verrucous endocarditis
C. Infective endocarditis
D. Large artery vasculitis

- **The answer is C: Infective endocarditis.** This patient meets the definition of fever of unknown origin (FUO), which requires recurring fevers >38.3°C for ≥3 weeks, without an established diagnosis. Many cases remain undiagnosed; however, this patient has a new murmur on cardiac examination and a valvular vegetation on echocardiography. Though blood cultures are often positive in

patients with endocarditis, there are certain organisms that can produce culture-negative infective endocarditis. *Coxiella, Bartonella,* and *Streptococcus* species are the most common causes. The HACEK organisms were previously thought to be the most common cause of culture-negative endocarditis; however, current blood culture techniques can isolate many of these organisms after 3 to 5 days. **(A)** Malignancy is always a concern in a patient with FUO, with common examples including leukemia, lymphoma, renal cell carcinoma, and abdominal cancers. **(B)** Verrucous endocarditis (Libman–Sacks endocarditis) will also present with negative blood cultures and is usually asymptomatic; it is associated with systemic lupus erythematosus (SLE) and the antiphospholipid syndrome; however, the negative tests for ANA and antiphospholipid antibodies rule out these diagnoses. **(D)** Vasculitides and other connective tissue diseases are causes of FUO, but these diagnoses are not suggested by the vignette.

B. Clinical Features

1. Manifestations that **may** accompany fever but are not specific to any specific entity
   a. Chills—paradoxical sensation of cold, often with shivering
   b. Rigors—severe form of chills with pronounced shivering and chattering of teeth
   c. Night sweats
   d. Change in mental status—especially at extremes of age
2. Look for systemic manifestations of some of the more common causes of FUO (e.g., skin changes, constitutional symptoms, anemia, weight loss)

***Quick* HIT**

FUO is obviously a term of exclusion, and is not itself a diagnosis. In patients with persistent unexplained fevers, continue diagnostic testing until the cause is found.

C. Diagnosis

1. Careful history and physical examination—with attention to medications, travel, occupational and environmental exposures, immune system competency, and a detailed review of systems
2. Laboratory tests
   a. CBC with differential
   b. Urinalysis
   c. Blood cultures. Ideally, three sets of blood cultures from different sites prior to antibiotics.
   d. Cultures of sputum, CSF, urine, and stool when indicated by clinical presentation.
   e. HIV immunoassay and HIV viral load if high risk
   f. Analysis and culture of abnormal fluid collections (e.g., joint, pleural)
   g. PPD or IGRA when latent TB is on the differential
   h. Other laboratory values: hepatic panel, ESR, CRP, CK, LDH, ANA, rheumatoid factor, TSH
3. Imaging studies
   a. CXR, CT scan of the chest and abdomen—to detect tumors and abscesses
   b. Nuclear scans are controversial but can be helpful in difficult cases to guide next steps in workup. FDG PET-CT scan can identify sites of occult malignancy and inflammation. Tagged WBC scan can be helpful but does not pinpoint a diagnosis.
   c. MRI, ultrasound, and echocardiogram may be appropriate, depending on the clinical situation
4. Invasive diagnostic procedures—excisional biopsy of lymph node, bone marrow, or other tissue when there is a high suspicion of tumor or abscess
5. Observation is sometimes necessary to make a diagnosis

D. Treatment

1. Antibiotics and corticosteroids may mask the patterns of fever response (see also Clinical Pearl 10-8). Base empiric treatment with antibiotics on the severity of illness.

2. If the patient is not acutely ill, observation may be all that is necessary to arrive at a specific diagnosis.
3. In many cases of FUO, fevers may resolve spontaneously without ever being diagnosed.
4. The sense of urgency in determining the cause of the fevers should be in proportion to the severity of illness and the host's immune status.

CLINICAL PEARL 10-8

Approach to Fever

- There is no uniformly accepted definition, but most sources define fever as body temperature >37.5°C (99.5°F) measured by a modern oral thermometer.
- Measurement—Readings obtained using rectal thermometers are slightly higher than oral or axillary thermometer readings.
- Hyperthermia versus fever.
  - Hyperthermia is an elevation in body temperature not caused by "raising the thermostat" (i.e., no change in the hypothalamic set-point).
  - Hyperthermia is usually caused by the inability of the body to dissipate heat.
  - Causes of hyperthermia include neuroleptic malignant syndrome, malignant hyperthermia, and heat stroke.
  - Hyperthermia does not respond to antipyretics, but rather to external cooling measures (e.g., ice, fans) and medications specific to the cause (e.g., dantrolene for malignant hyperthermia).
  - Fever occurs when there is an elevation in the hypothalamic set-point. It is a natural response to an inflammatory process.
  - Fever usually responds to antipyretics.
- Treat a fever with antipyretics when:
  - The fever is really hyperthermia.
  - The fever is dangerously high: >41°C (>105°F).
  - The patient is pregnant.
  - There is significant cardiopulmonary disease (increased oxygen demand may cause ischemia).
  - The patient wants symptomatic relief (chills, myalgias).

Toxic Shock Syndrome

A. General Characteristics

1. TSS is most commonly associated with menstruating individuals and tampon use, but can occur in all patients.
2. Other risk factors include surgical wounds, respiratory infections, burns, nasal packing, and infected insect bites.
3. It is caused by an enterotoxin of *S. aureus,* or less frequently an exotoxin of group A Streptococcus. **Note that it is the toxin rather than the bacteria that causes the pathology associated with TSS.**

Quick HIT

- The mortality rate for menstrual-related TSS is now <2% but is slightly higher (6%) for non–menstrual-related TSS.
- Previous TSS does **not** confer immunity. In fact, patients with a history of TSS are at greater risk for recurrent TSS.

B. Clinical Features

1. The onset of symptoms is characteristically abrupt
2. Symptoms may include:
   a. Flu-like symptoms: high fevers, headache, myalgias
   b. Diffuse macular, erythematous rash
   c. Hyperemic mucous membranes, “strawberry tongue”
   d. Warm skin due to peripheral vasodilation (see Chapter 1, Shock)
   e. Hypotension
   f. Nausea, vomiting, and diarrhea may also be present
3. By definition, there must be involvement of at least three organ systems, which may include:
   a. GI—nausea, vomiting, and diarrhea
   b. Hepatic—elevated bilirubin or transaminases
   c. Renal—elevations of BUN and/or creatinine, pyuria in absence of UTI
   d. Hematologic—thrombocytopenia
   e. Musculoskeletal—elevations of creatine kinase levels, severe myalgias

f. Mucous membranes—vaginal, oropharyngeal, or conjunctival hyperemia
g. CNS—confusion, disorientation (must be present when fever is absent)
4. Multisystem organ dysfunction or failure may occur
5. During the convalescent phase of illness (1 to 2 weeks after onset of rash), the **rash usually desquamates over the palms and soles**

C. Diagnosis

1. A high index of clinical suspicion is important.
2. Blood cultures are often negative. Other infectious pathogens (except for *S. aureus*) must be ruled out to diagnose TSS.
3. Cultures may be taken from the suspected source, but the diagnosis is primarily clinical.

D. Treatment

1. Hemodynamic stabilization is the first concern and often requires aggressive fluid resuscitation and/or vasopressors. Patient is often treated in a burn intensive care unit.
2. The source of toxin (e.g., tampon or nasal packing) should be removed immediately. Wounds may require drainage or debridement.
3. Give antistaphylococcal therapy, such as nafcillin, oxacillin, or vancomycin. Clindamycin is often used as adjunctive therapy. Include broad-spectrum gram-negative coverage (e.g., piperacillin-tazobactam, cefepime, or a carbapenem) for severely ill patients before causative organism is known.

Catheter-Related Bloodstream Infections (CRBSIs)

- Central venous catheters are a common cause of fever and sepsis in the hospital, especially in the ICU. When associated with a central line, they are referred to as central line–associated bloodstream infections (CLABSIs).
- The most common organisms are *S. aureus* and *Staphylococcus epidermidis.*

- Risk factors for CRBSI are emergent placement, femoral lines, total parenteral nutrition administration, and prolonged indwelling of the line.
- Only half of all patients with CRBSI have clinical evidence of infection **at the site of insertion** (i.e., erythema, purulence). Therefore, a high index of suspicion is required.
- If you suspect a CRBSI, promptly remove the catheter and send the tip for culture. This alone typically leads to resolution of fever and a decrease in leukocytosis. Antibiotics are usually initiated. Narrow the spectrum once the organism is identified.

***Quick* HIT**

Catheter-related bloodstream infections almost always involve central venous catheters. Peripheral venous catheters and arterial catheters are rarely involved.

***Quick* HIT**

- Neutropenia is defined by absolute neutrophil count (ANC) <1,500/mm^3 (ANC: combination of bands and mature neutrophils).
- Severe neutropenia is defined as ANC <500/mm^3 and corresponds to a severely increased risk of infection.

Neutropenic Fever

- Common causes include bone marrow failure (e.g., due to toxins, drugs, nutritional deficiencies, or infection), bone marrow invasion (e.g., from hematologic malignancy, metastatic cancer), and peripheral causes (e.g., hypersplenism, SLE, AIDS). Isolated neutropenia (agranulocytosis) is commonly caused by drug reactions.
- Because neutropenia severely compromises the patient's ability to mount an inflammatory response, fever may be the only manifestation of a raging infection.
- The most common infections seen in neutropenic individuals are transient bacteremia due to gut translocation of bacteria, cellulitis, and pneumonia.

- Obtain the following for any neutropenic patient with a fever: CXR, panculture (blood, urine, sputum, line tips, wound), CBC, complete metabolic panel.
- Place the patient on neutropenic precautions (hand hygiene, room with HEPA filtration, no plants or fresh flowers, and no rectal thermometers, enemas/suppositories, or digital rectal examinations).
- Give broad-spectrum antibacterial agents immediately after cultures are drawn.
- If fever persists beyond 4 to 7 days despite broad-spectrum antibacterial therapy, give antifungal agents, such as IV amphotericin B, echinocandin, or voriconazole. Consider G-CSF.

Miscellaneous Infections

Infectious Mononucleosis

A. General Characteristics

1. Caused by EBV (rarely by CMV which causes a similar clinical picture but is milder) (see also Table 10-13).
2. It is most commonly seen in adolescents and young adults, especially college students and military recruits (but may occur at any age). Infected children often experience milder symptoms or no symptoms.
3. Differential diagnosis in patients with fever, lymphadenopathy, and pharyngitis includes acute HIV infection, streptococcal infection, CMV, or toxoplasma infection.
   a. In pregnant patients, it is important to perform diagnostic tests as HIV, CMV, and toxoplasma infection can have adverse effects on the fetus.
4. Transmission
   a. The usual mode of transmission is through infected saliva (e.g., kissing, sharing food).
   b. Most adults (90%) have been infected with EBV and are carriers but infectious mononucleosis is uncommon in adults.
   c. One infection usually confers lifelong immunity.

d. The incubation period is typically 4 to 8 weeks.

B. Clinical Features

1. Symptoms
   a. Fever—temperatures may be as high as 40°C (104°F); fever usually resolves within 2 weeks
   b. Sore throat
   c. Malaise, myalgias, weakness—may linger for several months
2. Signs
   a. Lymphadenopathy—this is found in >90% of patients. Tonsillar or cervical (especially posterior cervical) lymph nodes may be quite enlarged, painful, and tender
   b. Pharyngeal erythema and/or exudate—frequently present
   c. Splenomegaly—present in half of patients
   d. Maculopapular or petechial rash—present in approximately 15% of patients, classically thought to develop after amoxicillin but can occur with other antibiotics or in the absence of antibiotics
   e. Hepatomegaly—in 10% of cases
   f. Palatal petechiae and eyelid (periorbital) edema—may occur in a minority of cases

Quick HIT

Infectious mononucleosis includes fever, fatigue, tonsillar pharyngitis, and lymphadenopathy.

TABLE 10-13 Common Organisms in Various Infections

Pneumonia	Community-acquired	
	Typical Atypical	*S. pneumoniae, H. influenzae, Moraxella catarrhalis, Mycoplasma* spp., *Chlamydia* spp., *Legionella* spp.
	Nosocomial	*S. aureus,* gram-negative rods
	Aspiration pneumonia	Oral anaerobes, gram-negative rods, *S. aureus*
Urinary Tract Infection		*E. coli, S. saprophyticus, Enterococcus, Klebsiella, Proteus* spp., *Pseudomonas, Enterobacter,* yeast (*Candida* spp.)
Osteomyelitis, Septic Arthritis		*S. aureus, S. epidermidis, Streptococcus* spp., gram-negative rods Consider *N. gonorrhoeae* in septic arthritis in adolescents
Skin/Soft Tissue	Surgical wound	*S. aureus,* gram-negative rods
	Diabetic ulcer	*S. aureus,* gram-negative rods, anaerobes
	Intravenous catheter site	*S. aureus, S. epidermidis*
	Cellulitis	*S. aureus,* group A streptococci
	Necrotizing fasciitis	*C. perfringens,* group A streptococci
Upper Respiratory	Pharyngitis	Viral, group A streptococci
	Acute bronchitis	Viral
	Acute sinusitis	Viral, *S. pneumoniae, H. influenzae, M. catarrhalis*
	Chronic sinusitis	*S. aureus,* anaerobes
Endocarditis	Subacute	*Streptococcus viridans*
	Acute	IV drug user: *S. aureus,* gram-negative rods, *Enterococcus* spp., yeast Prosthetic valve: *S. epidermidis*
Gastroenteritis		Viral, *Salmonella, Shigella, E. coli, C. botulinum, Giardia, Helicobacter* spp., *Campylobacter*
Intra-abdominal		*Enterococcus, Bacteroides fragilis, E. coli*
Meningitis		See Table 10-2.

Quick HIT

Common laboratory abnormalities include lymphocytosis and elevated aminotransferases.

Quick HIT

CMV Mononucleosis

- Most commonly seen in sexually active adolescents/young adults. Milder than EBV-associated IM.
- Characterized by fevers, chills, fatigue, headaches, and frequently, splenomegaly
- Cervical lymphadenopathy and pharyngitis usually absent or mild
- Negative for heterophile antibodies, frequently causes elevated transaminases

C. Diagnosis

1. Serology
   a. Monospot test—for detection of heterophile antibody
      - Heterophile antibodies are positive within 4 weeks of infection with EBV mononucleosis and are undetectable by 6 months. Thus, a positive monospot test indicates acute infection with EBV mononucleosis
      - Heterophile antibodies do not form in CMV mononucleosis
      - Rapid heterophile tests are highly sensitive and specific, particularly in adolescents

   b. EBV-specific antibody testing—perform in cases in which diagnosis is not straightforward (usually done by indirect immunofluorescence microscopy or by ELISA)
2. Peripheral blood smear—usually reveals lymphocytic leukocytosis with large, atypical lymphocytes
3. Throat culture—perform if pharyngitis is present to rule out a secondary infection with β-hemolytic streptococci

Quick HIT

If you suspect IM, order WBC count with differential and a monospot test. If monospot test is positive, no further testing needed. If negative and clinical suspicion is high, can repeat monospot test.

D. Complications

1. Hepatitis
2. Neurologic complications (rare): meningoencephalitis, Guillain–Barré syndrome, Bell palsy
3. Splenic rupture—rare
4. Thrombocytopenia, hemolytic anemia
5. Upper airway obstruction due to lymphadenopathy—rare

E. Treatment

1. In general, no specific treatment is indicated (or available) other than supportive care, as most people recover completely within 3 to 4 months. Supportive care includes:
   a. Rest, fluids
   b. Avoidance of strenuous activities and contact sports until splenomegaly resolves to prevent splenic rupture. This precaution applies to all patients, even those without splenomegaly on physical examination (low sensitivity for detecting splenomegaly)
   c. Analgesics to reduce temperature and pharyngeal pain—NSAIDs or acetaminophen
2. Give a short course of corticosteroids and consult ENT if there is airway compromise. Corticosteroids have also been effective in patients with fulminant liver failure, severe thrombocytopenia, or hemolytic anemia. They are not recommended for routine IM without complications
3. When to return to sports—concern is splenic rupture. Patients should wait 3 to 4 weeks from symptom onset before returning to sports as splenic rupture is very rare after 4 weeks

Diseases of the Skin and Hypersensitivity Disorders

11

Mark D. Duncan

KEY DEFINITIONS

- Note: exact size definitions vary, but below are common definitions used
  - **Dermatosis:** any cutaneous lesion/group of lesions; nonspecific term used to include any type of skin disease
  - **Dermatitis:** inflammation of the skin
  - **Macule:** circumscribed *flat* alterations in skin color ≤1 cm
  - **Patch:** a macule >1 cm
  - **Papule:** solid, **elevated** lesion with **no visible fluid** ≤0.5 cm
  - **Nodule:** a single lesion (papule) >0.5 cm
  - **Plaque:** discrete elevated lesions >0.5 cm, often formed by a confluence of papules
  - **Vesicle: fluid-filled** (serous fluid) lesions that are elevated and ≤0.5 cm
  - **Pustule: fluid-filled** (cloudy/purulent material of necrotic inflammatory cells)
  - **Bullae:** vesicle >0.5 cm
  - **Wheal:** rounded/flat-topped edematous elevation in the skin; often erythematous
  - **Telangiectasia:** visible, dilated blood vessel in the superficial skin that blanches
  - **Petechiae:** small (1 to 2 mm), nonblanching erythematous macules that result from microhemorrhages
  - **Ecchymosis:** nonblanching and nonpalpable red/purple discoloration of the skin that results from extravasation of blood into the skin
  - **Palpable purpura:** palpable, nonblanching red/purple discoloration of the skin that results from extravasation of blood into the skin with an inflammatory etiology (i.e., vasculitis)

COMMON SKIN DISORDERS

Acneiform Eruptions

Acne Vulgaris

A. General Characteristics

1. Acne vulgaris is an inflammatory condition of the skin that is most prevalent during adolescence
2. Pathogenesis is multifactorial:
   a. Follicular hyperkeratinization
   b. Increased sebum production
   c. Obstruction of sebaceous follicles (by sebum) leads to the proliferation of *Cutibacterium acnes* (an anaerobic bacterium, formerly known as *Propionibacterium acnes*) in the sebum
   d. Inflammation as a result of *C. acnes* proliferation
3. Risk factors are male sex, puberty, Cushing syndrome, oily complexion, androgens (due to any cause), and medications. Genetics also plays a role
4. Classification:
   a. Obstructive acne: closed comedones (whiteheads) or open comedones (blackheads)
   b. Inflammatory acne: Lesions progress from papules/pustules to nodules, then to cysts, then scars

FIGURE 11-1 **Comedonal acne.**
(Reprinted with permission from White AJ. *The Washington Manual of Pediatrics*. 2nd ed. Wolters Kluwer; 2016. Figure 15-13A.)

***Quick* HIT**

- There is no proven link between acne and chocolate, though other foods (milk, high glycemic load diets) have an association.
- Oral contraceptives (especially some of the newer oral contraceptive pills) help some women with acne.

B. Treatment

1. General guidelines:
   a. Instruct patient to keep affected area clean (vigorous washing is unnecessary); reduce or discontinue acne-promoting agents (certain make-up, creams, oils, steroids, androgens).
   b. It takes about 6 weeks to notice the effects of medications (skin may get worse before it gets better). Start with one drug to assess its efficacy.

2. Mild-to-moderate acne (Figure 11-1):
   a. Begin with a topical retinoid, or add topical benzoyl peroxide (2.5%) if there are also papulopustular lesions. Topical retinoids increase cell turnover and peeling of skin, which prevents clogging of pores. Topical benzoyl peroxide prevents plugging of pores and kills acne-causing bacteria.
   b. Add topical retinoids if the above fails. They cause peeling of the skin, which prevents clogging of pores.
   c. Add topical clindamycin or topical dapsone—both act to suppress *C. acnes.*
3. Moderate-to-severe nodular pustular acne (Figure 11-2):
   a. Oral retinoids (e.g., isotretinoin) should be considered early. Oral retinoids are extremely teratogenic. All female patients must have two negative pregnancy tests before starting oral isotretinoin. In addition, they should use two forms of birth control for 1 month before starting the medication through 1 month after stopping the medication.
   Other options include an oral tetracycline class antibiotic, or in females either oral contraceptives or oral spironolactone.

Quick HIT

Oral isotretinoin should be considered early in the course of severe acne, since it is the only treatment that can induce long-term remission.

Rosacea

- A chronic condition resulting in reddening of the face (mainly the forehead, nose, and cheeks). It often appears very similar to acne, but unlike acne it first starts in middle age.
- Mostly affects Caucasian women between 30 and 50 years of age.
- The most common skin findings include erythema, telangiectasia, papules, and pustules with redness, typically affecting the face. Unlike acne vulgaris, there are no comedones (Figure 11-3).
- In severe cases, skin can become thickened and greasy—on the nose, it creates a bulbous appearance called rhinophyma (mostly seen in men).

- Treatment of erythema and flushing: avoid alcohol, hot beverages, extremes of temperature, and emotional stressors. If inadequate, topical brimonidine can be used.
- Treatment of papules and pustules: start with topical metronidazole gel; alternatives are azelaic acid and topical ivermectin. If inadequate, may add systemic antibiotics (e.g., tetracycline), and then oral isotretinoin as a last option.

FIGURE 11-2 **Severe nodulocystic acne.**
(Courtesy of Robert I. Rudolph, MD. From Goodheart HP. *Goodheart's Same-Site Differential Diagnosis*. 2nd ed. Wolters Kluwer; 2022. Figure 7-14.)

Hidradenitis Suppurativa

- Inflammatory skin condition affecting intertriginous areas (axilla is the most common site), causing nodules, abscesses, and draining sinus tracts that can result in scarring.
- More common in women, and typical onset in second or third decade of life. Strong relationship with smoking.
- Pathogenesis includes follicular occlusion and subsequent rupture, leading to acute inflammation.
- Treatment is based on severity of disease. For mild disease, topical clindamycin may be used. For moderate disease, oral antibiotics, oral retinoids, or hormonal therapy may be used; if these are inadequate, adalimumab may be used. For severe extensive disease, surgical excision is often required.

Atopic and Contact Dermatitis

Atopic Dermatitis (Eczema)

- The terms "dermatitis" and "eczema" are often used interchangeably. There are several common dermatoses (atopic dermatitis, contact dermatitis, stasis dermatitis, etc.) that involve dry, inflamed, and pruritic lesions. The term eczema most commonly refers to atopic dermatitis.
- Eczema is more frequent in children but also occurs in adults and commonly involves flexor surfaces (e.g., antecubital and popliteal fossae, wrists). It is commonly associated with a personal or family history of atopy (seasonal allergies, asthma).
- Management involves first eliminating triggers (allergens, frequent bathing without moisturizing, heat, low humidity) and adjuncts such as antihistamines for pruritus. Topical steroids should be used for affected areas, with the potency of steroids chosen based on severity. Topical calcineurin inhibitors (i.e., tacrolimus) can be used if there is an inadequate response to high potency steroids.

FIGURE 11-3 **Rosacea.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 1.14.)

Contact Dermatitis

A. General Characteristics

1. There are two forms of contact dermatitis: irritant and allergic.
2. Irritant contact dermatitis is more common and results from a chemical or physical insult to the skin (e.g., contact with detergents, acids, or alkalis, or from frequent hand washing).
   a. A previous sensitizing event is not needed to produce the rash (i.e., it is not an immunologic reaction).
   b. The rash begins shortly after exposure to the irritant (in contrast to the allergic type, which begins several hours to a few days later).
3. Allergic contact dermatitis is **a delayed-type hypersensitivity (type IV) reaction.**
   a. No history of atopy is necessary for allergic contact dermatitis to occur. It can occur in anyone.

b. Sensitization of the skin occurs 1 to 2 weeks after the first exposure to the allergen. Subsequent exposure leads to dermatitis hours to days after the reexposure. Therefore, dermatitis develops only in patients who have already been sensitized to the allergen. Common allergens include poison ivy, oak, and sumac; iodine; nickel; rubber; topical medications (e.g., neomycin, topical anesthetics); and cosmetics.

Quick HIT

Do not confuse allergic contact dermatitis with any of the following:

- Irritant contact dermatitis—rash is usually identical to that seen in allergic contact dermatitis, except the rash begins very soon after exposure
- Atopic dermatitis—onset is in infancy or childhood
- Seborrheic dermatitis
- Psoriasis

B. Clinical Features

1. The appearance of the rash depends on the stage.
   a. Acute stage: erythematous papules and vesicles with oozing; edema may be present.
   b. Chronic stage: crusting, thickening, and scaling; lichenification.
2. The rash is usually very pruritic and is found only in exposed areas.
3. The interval between exposure and appearance of the rash varies, but is usually from several hours to as long as 4 to 5 days.

C. Diagnosis

1. Diagnosis is usually made clinically based on history and examination.
2. Patch testing (to identify the allergen that caused the allergic reaction) is indicated if the diagnosis is in doubt, the rash does not respond to treatment, or the rash recurs.

D. Treatment

1. Avoid the contact allergen!
2. Apply cool tap water compresses
3. Apply topical corticosteroids

4. Prescribe systemic corticosteroids (e.g., prednisone, 1 mg/kg/day) for severe cases. Continue for 10 to 14 days and then taper

Papulosquamous Eruptions

Psoriasis

A. General Characteristics

1. Psoriasis is due to abnormal (markedly accelerated) proliferation of skin cells. Because of this, the skin does not have time to mature normally. This leads to defective keratinization, which causes the scaling.
2. The cause is unknown, but genetics are believed to be important.
3. This is a chronic condition characterized by exacerbations and remissions—it improves during the summer (sun exposure) and worsens in the winter (dries skin).
4. Trauma to the skin (e.g., infection, abrasion) can cause local flares at the site of injury, which is termed the Koebner phenomenon.
5. Up to three-fourths of patients have somewhat localized disease (<20% to 25% of body surface area [BSA]).
6. **Less than 10% of patients develop psoriatic arthritis** (see Chapter 6).

FIGURE 11-4 **Psoriasis.**
(Courtesy of David Sheinbein, MD. From Council ML, Sheinbein DM, Cornelius LA. *The Washington Manual of Dermatology Diagnostics*. Wolters Kluwer; 2016. Figure 3-8A.)

Quick HIT

There is no cure for psoriasis, but the disease can be managed.

B. Clinical Features

1. The most common clinical subtype is chronic plaque psoriasis; other variations include pustular psoriasis, guttate psoriasis, nail psoriasis, and others.
2. Lesions are well-demarcated, erythematous papules or plaques that are covered by thick, *silvery scaling;* pruritus is rarely present (Figure 11-4).
3. *Auspitz sign*—removal of the scale causes pinpoint bleeding.
4. It can involve any part of the body, but the most common areas are the **extensor surfaces of extremities (knees, elbows),** scalp, intergluteal cleft, palms, and soles.
5. Pitting of the surface of nails, or onycholysis (distal separation of the nail from the nail bed).

C. Treatment

1. Topical therapy
   a. Corticosteroids and emollients are the most commonly prescribed first-line agents.
   b. Calcipotriene and calcitriol are vitamin D derivatives that have become first- or second-line agents. They are very effective in most patients.
   c. Tars have an unpleasant odor, so they are less desirable to use. Patients should use tars for 4 to 6 weeks before expecting to see a benefit. Tars are more effective in combination therapy and are associated with an 80% to 90% remission rate.
   d. Other options include tazarotene (a vitamin A derivative), anthralin, and topical calcineurin inhibitors.
   e. Combination therapy (e.g., steroids and calcipotriene) is more effective than either agent alone.
   f. Phototherapy (with ultraviolet light) should be used for moderate–severe psoriasis if feasible.

2. Systemic treatment is indicated in patients with severe psoriasis. Options include immune-modulating therapy (e.g., methotrexate, infliximab, cyclosporine, etanercept), oral retinoids (e.g., acitretin), and combinations of these agents with phototherapy.

Quick HIT

Oral steroids should be avoided in psoriasis, since discontinuation can cause flaring and can precipitate erythroderma.

A 22-year-old man with a history of asthma presents with a 2-day history of several small and scaling erythematous papules and plaques on his torso, back, and all four extremities. The patient reports that 3 weeks ago he had an unrelenting sore throat that just recently resolved. The patient has never had this skin condition before and denies a family history of psoriasis or any other dermatologic condition.

Which of the following is the likely diagnosis?

A. Plaque-like psoriasis
B. Pustular psoriasis
C. Guttate psoriasis
D. Erythrodermic psoriasis

- **The answer is C: Guttate psoriasis.** The patient's clinical presentation in this question is consistent with a diagnosis of guttate psoriasis. Guttate psoriasis is the second most common form of psoriasis and accounts for less than 10% of cases. Dermatologic examination reveals numerous small and scaling erythematous papules and plaques on the torso and extremities. This type of psoriasis often follows streptococcal pharyngeal infection, so patients should be asked about a recent sore throat or diagnosis of streptococcal pharyngitis. **(A)** Plaque-like psoriasis is the most common form of psoriasis (nearly 90%) and is characterized by sharply demarcated erythematous scaling plaques, commonly on the elbows, knees, and scalp. **(B, D)** Pustular and erythrodermic psoriasis are the most severe forms of psoriasis as they both can compromise the protective functions of the skin (temperature control, fluid maintenance, electrolyte balance). Pustular psoriasis is associated with pus-filled blisters rather than plaques. Erythrodermic psoriasis, unlike the other types of psoriasis, usually affects the entire body and gives the skin a "burned" appearance.

Seborrheic Dermatitis

A. General Characteristics

1. A chronic, idiopathic, inflammatory skin disorder that occurs in all age groups.
2. Very common problem (affects 5% of the population), especially in patients with **oily** skin.
3. Exacerbating factors: anxiety, stress, fatigue, hormonal factors.
4. Common locations: scalp (dandruff), hairline, behind ears, external ear canal, folds of skin around nose, eyebrows, armpits, under breasts, groin area (skin folds).
5. May be complicated by secondary bacterial infection.

***Quick* HIT**

Seborrheic dermatitis is a chronic condition with no cure. Therapy may be needed indefinitely for control of symptoms.

B. Clinical Features

1. Mild cases manifest as dandruff.
2. Severe cases yellowish, oily, and thick flakes appear near eyelashes, in the ear canal, on the middle chest, behind the ears, and other skin folds.
3. Scaly patches with surrounding areas of mild-to-moderate erythema (Figure 11-5).
4. Usually asymptomatic, but pruritus, skin lesions, and hair loss can occur if left untreated.

C. Treatment

1. Sunlight exposure often helps.
2. Dandruff shampoo (over-the-counter) is usually adequate.
3. Topical ketoconazole (to decrease yeast count on skin) has been found to be effective.
4. Topical corticosteroids for severe cases.

Pityriasis Rosea

- Papulosquamous eruption—initially, "herald patches" that resemble ringworm (multiple round/oval patches) appear, and then a generalized rash with multiple oval-shaped lesions appears. **The rash is classically described as having a Christmas tree–type appearance** (Figure 11-6).
- It is **not** contagious and is possibly related to herpes type 7.
- It is common on the trunk and upper arms and thighs, and is usually not found on the face. Pruritus is often present, and varies in severity.
- It spontaneously remits within a few (6 to 8) weeks without treatment. There is no treatment other than antihistamines for pruritus. Recurrences are rare.

FIGURE 11-5 **Seborrheic dermatitis.**
(Reprinted with permission from Goodheart HP. *Goodheart's Same-Site Differential Diagnosis: A Rapid Method of Diagnosing and Treating Common Skin Disorders*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010.)

Lichen Planus

- Chronic, inflammatory mucocutaneous lesions of unknown etiology. It may be associated with hepatitis C and certain drugs.
- (4 Ps): **P**ruritic, **p**olygonal, **p**urple, flat-topped **p**apules.
- Most commonly seen on wrists, shins**, oral mucosa,** and genitalia.
- Treat with steroids.

Allergic Reactions

Urticaria (Hives)

- Urticaria is caused by the release of mediators from mast cells, with a resultant increase in vascular permeability. It may be acute (<6 weeks) or chronic.
- Urticaria can be precipitated by food, drugs, latex, animal dander, pollen, dust, plants, infections, cold/heat, and certain medical conditions (e.g., hypocomplementemic urticarial vasculitis).
- Findings—migratory edematous wheals (hives) that often quickly appear and then disappear. They blanch with pressure, and may cause intense pruritus or stinging. Lesions get worse with scratching (Figure 11-7).
- Treatment involves removal of the offending agent. Antihistamines are effective for symptomatic relief. Systemic corticosteroids may help in more severe cases.

FIGURE
11-6 **Pityriasis rosea.**
(Reprinted with permission from Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Lippincott Williams & Wilkins; 2004. Figure 6.23A.)

FIGURE 11-7 Urticaria.
(Reprinted with permission from Elder DE. *Atlas of Dermatopathology: Synopsis and Atlas of Lever's Histopathology of the Skin*. 4th ed. Wolters Kluwer; 2020. Clin. Fig. VA3.a.)

Quick HIT

Unlike erythema multiforme, urticaria has a clear or pink center and is blanchable.

Quick HIT

Hereditary angioedema: autosomal dominant condition caused by C1 esterase inhibitor deficiency, characterized by recurrent episodes of angioedema; can be life-threatening

- Angioedema can involve the GI tract, causing nausea/vomiting and abdominal pain (can be so severe as to mimic acute abdomen).
- **Severe angioedema can lead to potentially life-threatening airway obstruction.**
- Treatment is similar to treatment of urticaria. Give SC epinephrine for laryngeal edema or bronchospasm.

Angioedema

- The mechanism is similar to that in urticaria, though angioedema occurs deeper in the skin (i.e., fluid extravasation occurs in deeper layers of skin/subcutaneous tissue). Angioedema and urticaria can occur simultaneously or independently.
- Angioedema can be caused by any of the precipitants of urticaria. **ACE inhibitors** are a specific cause of angioedema (reaction usually occurs within 1 week of initiating the drug).
- Unlike urticaria, which can occur anywhere, angioedema usually affects the eyelids, lips and tongue, genitalia, hands, or feet.
- Angioedema results in nonpitting, puffy skin with firm swelling that is more tender and "burning" than pruritic (because there are fewer mast cells/sensory nerve endings in deeper tissues)

Anaphylaxis

- The most severe form of allergy, anaphylaxis is a systemic, life-threatening allergic reaction caused by a massive release of mast cell mediators (usually a type I hypersensitivity reaction) that occurs within seconds to minutes.
- Numerous causes have been identified, including foods **(most common cause)**, medications, radiocontrast agents, blood products, venoms (e.g., from snakes), insect stings, latex, hormones, ragweed/molds, and various chemicals.

- Clinical findings include **skin and mucosal signs** (most common and early findings; urticaria, swollen lips and tongue, periorbital edema), **respiratory signs** (dyspnea, wheeze, airway obstruction), **GI signs** (nausea/vomiting, crampy abdominal pain), and **cardiovascular signs** (tachycardia, hypotension, shock).
- Treatment of anaphylaxis:
  - ABCs—secure the airway (intubation may be necessary) and provide supplemental oxygen, treat hypotension with rapid infusion of IV fluids.
  - Give IM epinephrine immediately; may require several doses of 0.3 to 0.5 mg (1 mg/mL preparation). If not responding, prepare IV epinephrine infusion.
  - If still wheezing despite epinephrine, give albuterol for bronchospasm.
  - Adjuncts to consider: antihistamines (both H_1 and H_2 blockers such as diphenhydramine and ranitidine) and corticosteroids. These are less important for the acute management of anaphylaxis.

CLINICAL PEARL 11-1

Types of Hypersensitivity Reactions

- **Type I:** IgE-mediated (e.g., anaphylaxis, asthma)
- **Type II:** IgG- (or IgM-) and cytotoxic cell-mediated (e.g., Goodpasture disease, pemphigus vulgaris)
- **Type III:** antigen–antibody complexes (e.g., SLE, Arthus reaction, serum sickness)
- **Type IV:** T-cell–mediated (delayed hypersensitivity) (e.g., allergic contact dermatitis, tuberculosis, transplant rejection)

Drug Reactions

Overview

- An adverse drug reaction is not necessarily an allergic drug reaction (see also Clinical Pearl 11-1). Adverse drug reactions include drug side effects, drug–drug interactions, drug toxicity and associated illnesses, and drug

allergy. Most cases of adverse drug reactions are **not** related to allergy (only 10% have a true allergic basis).

- Many patients who state they are "allergic" to a medication believe themselves to be allergic because they have been incorrectly labeled without direct immunologic evidence. However, given the serious risks of a true drug allergy, one should avoid the suspected medication.
- β-Lactam antibiotics (penicillins), aspirin, NSAIDs, and sulfa drugs account for more than 80% of all cases of drug allergy. Other drugs implicated include insulin, local anesthetics, ACE inhibitors, and radiocontrast agents.
- Drug-induced hypersensitivity reactions most commonly manifest as type IV reactions with diffuse maculopapular eruptions; however, all four hypersensitivity mechanisms can serve as the underlying mechanism, and clinical findings can vary widely and can affect multiple organ systems (interstitial nephritis, pneumonitis, cardiovascular collapse from anaphylaxis, etc.).

Quick HIT

- **Allergic reactions typically appear within 1 month of initiating the drug.** It is uncommon for a drug reaction to occur within less than 1 week of initiating the drug.

Fixed Drug Eruption

- Typically caused by antibiotics or NSAIDs, fixed drug eruption characteristically appears early (within hours) after reexposure to the precipitating medication in the same body location.
- A purple patch will typically appear, and upon reexposure more lesions can develop. The lesions typically resolve spontaneously, leaving an area of postinflammatory hyperpigmentation.

Acute Generalized Exanthematous Pustulosis (AGEP)

- AGEP presents with fever, leukocytosis, and a skin eruption of small pustules on an erythematous background. The eruption typically occurs within hours or days after exposure to the drug, and typically begins on the face and neck and then spreads to the trunk and limbs.

- Antibiotics are the most common culprit, and treatment is supportive (discontinuing the medication and topical steroids).

Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)

- A systemic reaction that typically occurs 2 to 6 weeks after starting a medication (longer latency than other drug reactions). Initial symptoms include fever, lymphadenopathy, facial edema, and a diffuse, morbilliform skin eruption. The reaction can progress to involve multiple organ systems, most commonly the liver, kidneys, and lung.
- The most common precipitating medications are allopurinol, antiepileptics, sulfa drugs, vancomycin, minocycline, and dapsone.
- Diagnosis is made using a clinical scoring system based on history of exposure to a common medication, typical examination findings (e.g., fever, morbilliform eruption), and laboratory abnormalities (eosinophilia, abnormal liver enzymes, acute kidney injury).
- After withdrawal of the offending agent, treatment may involve steroids if there is significant lung or kidney involvement, and liver involvement can sometimes progress to acute liver failure requiring transplant.

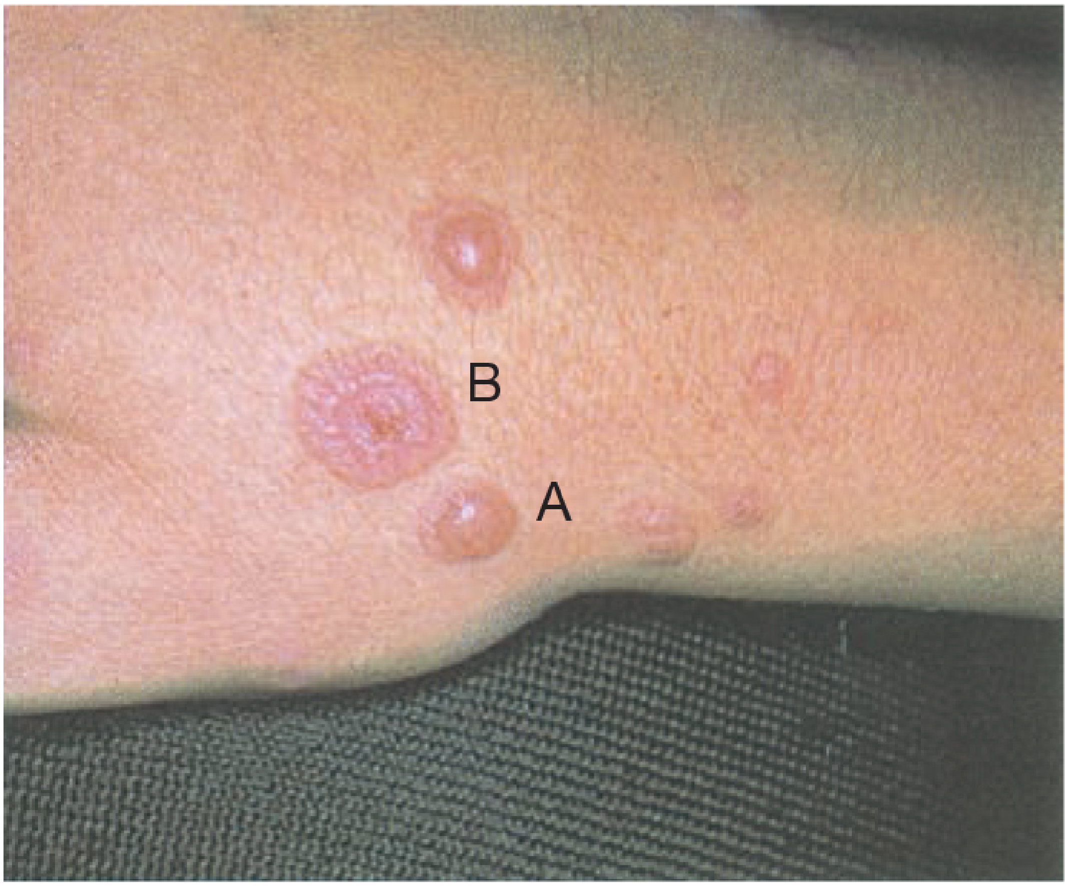


FIGURE 11-8 **Erythema multiforme. A: Bulla. B: Target (or iris) lesion.**
(Reprinted with permission from Bickley LS, Szilagyi PG. *Bates' Guide to Physical Examination and History Taking*. 8th ed. Lippincott Williams & Wilkins; 2003. Table 4.8.)

***Quick* HIT**

EM is caused by infection in 90% of cases. Viral, bacterial, and fungal infections can all cause EM, but two common (and commonly tested) associations are HSV and Mycoplasma.

- Treatment is directed at the underlying etiology (e.g., acyclovir for HSV). Topical steroids and oral antihistamines are used for symptomatic relief; oral steroids can be used for more severe cases.

Erythema Multiforme

- Erythema multiforme (EM) is an inflammatory skin condition that can be described as EM minor (mild or no mucosal involvement, no systemic

symptoms) or EM major (severe mucosal involvement and systemic symptoms). EM major is a distinct entity from Stevens–Johnson syndrome (SJS).

- EM is characterized by erythematous macules/papules that resemble target lesions **("bull's-eye lesions")** that can become bullous (Figure 11-8). Skin lesions may be pruritic and painful, and often affect the palms, soles, and mouth.
- EM can be caused by medications, though the **majority of cases are caused by infections** (especially HSV). The most common precipitating medications are antibiotics, sulfa drugs, antiepileptics, and NSAIDs. Other causes of EM include autoimmune disease, malignancy, vaccines, and radiation.

***Quick* HIT**

The "rule of nines" is the quickest method of estimating the affected BSA—the head is 9%, each arm is 9%, each leg is 18%, and each side of the trunk (anterior and posterior) is 18% (e.g., for a rash covering both arms and half the chest, the total affected BSA is 27%). Alternatively, for smaller areas, the palm and fingers together are 1%.

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

- SJS and TEN are part of a disease continuum of severe mucocutaneous eruptions. They are dermatologic emergencies.
- SJS involves <10% BSA, and TEN involves >30% BSA. SJS/TEN overlap describes patients with 10% to 30% BSA involvement.
- The majority of cases are caused by medications (most commonly antiseizure medications, sulfa antibiotics, allopurinol, nevirapine, and NSAIDs), though up to a third of cases have no apparent trigger. Mycoplasma is a known infectious precipitant.
- Skin lesions are typically coalescing erythematous macules and target lesions that progress to vesicles/bullae with extensive skin necrosis and sloughing. Mucosal involvement is very common in both SJS and TEN.
- **Potentially life-threatening** (mortality rate is 10% for SJS and 30% for TEN). Other complications include massive fluid and electrolyte loss, secondary infections and sepsis, and multiorgan failure.

- Management: admit to ICU or burn unit. Withdraw the suspected medication; aggressive rehydration and symptomatic management. Urgent dermatology and ophthalmology consultation is indicated.

Erythroderma

- A life-threatening dermatologic emergency that causes erythema and scaling that involves 90% or more of the patient's BSA.
- Erythroderma may be caused by medications or a flare of an existing dermatitis (such as atopic dermatitis or psoriasis, especially after abrupt discontinuation of oral steroids). A large number of cases are idiopathic. Other less common associations include the Sezary syndrome (cutaneous T-cell lymphoma), other hematologic and solid-organ malignancies, autoimmune disease (lupus), and infections.
- Treatment involves intensive skin care (emollients, dressings, warm and humid environment), oral antihistamines and topical steroids, and addressing the underlying condition.

FIGURE 11-9 **Erythema nodosum.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 25.17.)

Other Inflammatory and Autoimmune Disorders

Erythema Nodosum

- Erythema nodosum appears as painful, red, subcutaneous, elevated nodules, typically located over the anterior aspect of the tibia (less commonly on the trunk or arms) (Figure 11-9). It is self-limited and usually resolves within a few weeks. Low-grade fever, malaise, and joint pain may precede the rash.
- It is much more common in women (especially young women) than in men.
- Many causes: *Streptococcus* infection, tuberculosis, other bacterial, viral, and fungal infections, sarcoidosis, inflammatory bowel disease, Behçet disease, pregnancy, medications (e.g., oral contraceptives, sulfa drugs, amiodarone, antibiotics), syphilis, tuberculosis, malignancy, and others. Many cases are idiopathic.
- Perform the following to help determine the underlying condition: chest radiograph (for sarcoidosis, tuberculosis, other infections), antistreptolysin-O titer, CBC, erythrocyte sedimentation rate and C-reactive protein, and tuberculin skin test or interferon-gamma release assay. Additional tests should be based on patient factors (pregnancy test in females, STI screen, etc.).
- Treat the underlying condition, if known.
- Bed rest, leg elevation, and heat for symptoms. NSAIDs or potassium iodide may help.

A 41-year-old woman presents with tender and enlarged lumps on her shins. She also endorses weakness, subjective fevers, and arthralgia. On physical examination, several tender, erythematous nodules are palpated on the dorsal aspect of the legs.

Which of the following is NOT associated with this dermatologic condition?

A. Sarcoidosis
B. Inflammatory bowel disease
C. Streptococcal infection
D. Diabetes mellitus type 2

- **The answer is D: Diabetes mellitus type 2.** The patient in this question is presenting with erythema nodosum, inflammatory lesions of subcutaneous fat that are usually located on the shins. The nodules are usually tender and typically resolve in 1 to 2 months. **(A, B, C)** All these conditions are associated, except for diabetes mellitus.

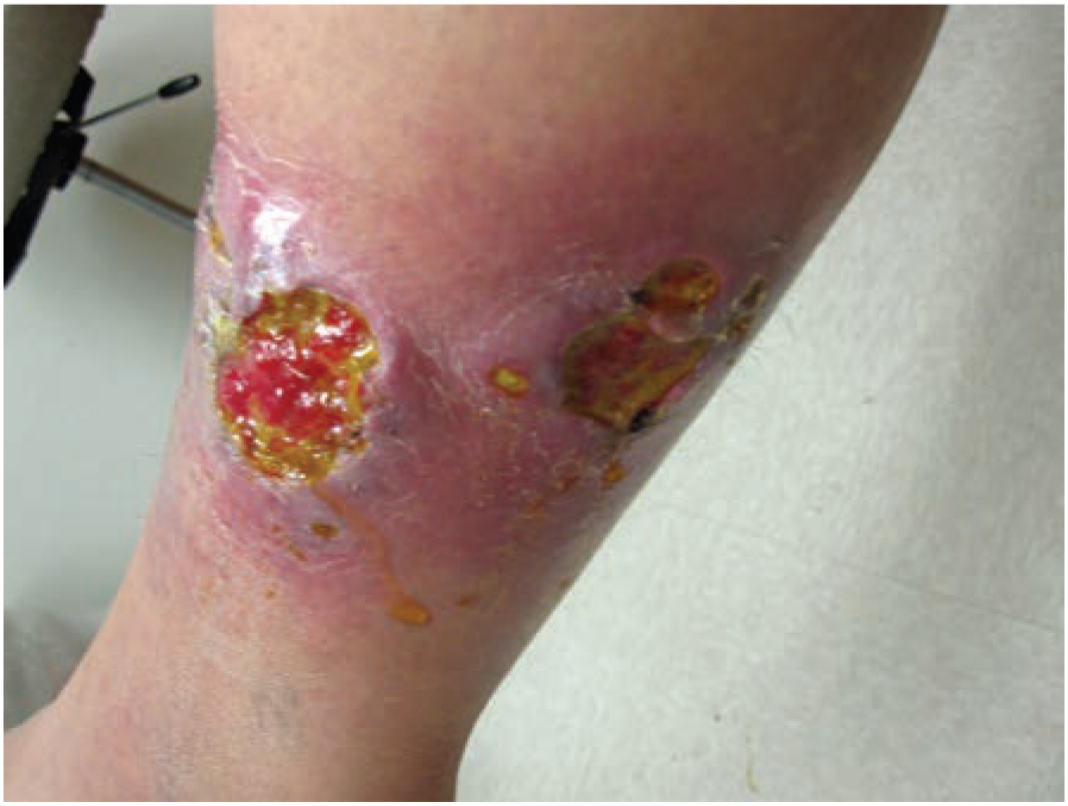


FIGURE 11-10 **Pyoderma gangrenosum.**
(Reprinted with permission from Goodheart HP, Gonzalez ME. *Goodheart's Photoguide to Common Pediatric and Adult Skin Disorders*. 4th ed. Wolters Kluwer; 2015. Figure 29-6.)

Pyoderma Gangrenosum

- A neutrophilic dermatosis that most commonly presents with ulcerating lesions that display pathergy (trauma makes the lesion worse, so avoid debridement) (Figure 11-10).
- Pyoderma gangrenosum is commonly associated with IBD, hematologic disease (especially IgA monoclonal gammopathy), and rheumatologic disease (rheumatoid arthritis, seronegative spondyloarthritis, and others).
- Treatment involves nontraumatic wound care and topical agents (high potency steroids or tacrolimus). If severe or fails to respond to initial measures, then alternatives include systemic dapsone or minocycline, or immunomodulating therapies such as cyclosporine.

Bullous Pemphigoid

- Multiple subepithelial blisters on abdomen, groin, and extremities (Figure 11-11).
- Elderly people are most commonly affected.
- Blisters are less easily ruptured than in pemphigus vulgaris.
- Autoimmune condition; no malignant potential but may be persistent.
- Treat with systemic or topical glucocorticoids.

A 57-year-old man presents with a blistering rash on his chest and upper arm. He reports that the blisters often erupt and are mildly pruritic. He denies oral lesions. Nikolsky sign is negative. Biopsy is performed which reveals linear immunofluorescence of the epidermal basement membrane.

Which of the following is the underlying mechanism of this disease?

A. IgG antibodies against desmosomes
B. Deposits of IgA at the tips of dermal papillae
C. Type IV hypersensitivity reaction following exposure to allergen
D. IgG antibodies against hemidesmosomes

- **The answer is D: IgG antibodies against hemidesmosomes.** The patient in this question is presenting with signs and symptoms consistent with bullous pemphigoid. Given that Nikolsky sign (separation of the epidermis with lateral stroking of the skin) is negative and the biopsy demonstrated linear immunofluorescence of the epidermal basement membrane, bullous pemphigoid is more likely than pemphigus vulgaris. The underlying mechanism of this autoimmune disease involves IgG antibodies against hemidesmosomes (located on the epidermal basement membrane). Bullous pemphigoid often spares the oral mucosa and presents with tense blisters. **(A)** IgG antibodies against desmosomes is the mechanism underlying pemphigus vulgaris (PV), which has a higher mortality. Immunofluorescence studies in PV reveal antibodies around keratinocytes in a netlike pattern (intraepidermal separation rather than subepidermal separation associated with bullous pemphigoid). Furthermore, blisters tend to be flaccid in PV and Nikolsky sign is positive. **(B)** IgA deposition in the dermal papillae is the mechanism underlying dermatitis herpetiformis, which is associated with celiac disease. **(C)** A Type IV hypersensitivity reaction following exposure to an allergen is consistent with allergic contact dermatitis.

FIGURE 11-11 **Bullous pemphigoid.**
(Reprinted with permission from Elder DE. *Atlas of Dermatopathology: Synopsis and Atlas of Lever's Histopathology of*

the Skin. 4th ed. Wolters Kluwer; 2020. Clin. Fig. IIIA1a.c.)

Pemphigus Vulgaris

- Autoimmune blistering condition resulting in loss of normal adhesion between cells (acantholysis)
- Starts in oral mucosa; may become generalized.
- Blisters rupture, leaving painful erosions.
- Most commonly affects elderly people, **often fatal if untreated.**
- Autoantibodies (usually IgG) directed against the adhesion molecule desmoglein.
- Treat with systemic glucocorticoids and other immunosuppressants.
- Pemphigus may be the presenting symptoms of malignancies such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease.

Vitiligo

- Chronic, depigmenting condition due to unknown cause; hereditary component is suspected
- Sharply demarcated areas of skin become amelanotic—most common on the face
- Associated with diabetes mellitus, hypothyroidism, pernicious anemia, and Addison disease
- Topical glucocorticoids and photochemotherapy are used to promote repigmentation with varying degrees of success

SKIN CONDITIONS RELATED TO INFECTIONS AND INFESTATIONS

Warts

A. General Characteristics

1. Warts are caused by HPV and are transmitted via skin-to-skin contact. For genital warts, transmission is via intimate sexual contact.
2. Types
   a. **The common wart (*Verruca vulgaris*)—most common type.**
      - May occur anywhere, but the most common sites include elbows, knees, fingers, and palms.
      - Appearance: flesh-colored or whitish with a hyperkeratotic surface.

   b. The flat wart (*Verruca plana*).
      - Common sites include the chin/face, dorsum of hands, and legs.
      - Appears flesh-colored with smooth papules and a flat surface.

   c. The plantar wart (*Verruca plantaris*).
      - Solitary or multiple warts found on the plantar side of the foot; can cause foot pain if located on pressure areas (e.g., metatarsal head, heel).
      - Appearance: flesh colored with a rough, hyperkeratotic surface.

   d. Anogenital wart (*Condyloma acuminatum*).
      - **Most common STI**, commonly associated with HPV 6 and 11 (Figure 11-12).
      - HPV (types 16, 18) infection can lead to cervical cancer in women (Pap smear is important), and protective vaccines are available.
      - Appearance: single or multiple soft, fleshy growths on the genitalia, perineum, and anus.

***Quick* HIT**

Most warts disappear spontaneously within 1 to 2 years. However, if the condition is left untreated, more warts can appear.

FIGURE
11-12 **Human papilloma virus (genital wart).**
(Reprinted with permission from Wilkinson EJ, Stone IK. *Atlas of Vulvar Disease*. Williams & Wilkins; 1994. Figure 17.9A.)

FIGURE 11-13 **Molluscum contagiosum.**
(Reproduced from Centers for Disease Control and Prevention: Molluscum Contagiosum. Available at: http://www.cdc.gov/poxvirus/molluscum-contagiosum.)

***Quick* HIT**

Warts can be recurrent and may require multiple treatments (despite the method of therapy chosen).

B. Treatment

1. First line is typically salicylic acid or cryotherapy (freezing with liquid nitrogen).
2. For refractory warts, options include 5-FU, intralesional bleomycin, topical or intralesional immunotherapy (e.g., *Candida* antigen), surgical therapy, laser therapy, imiquimod, and many others.

Molluscum Contagiosum

- A common, self-limited viral infection caused by a **poxvirus;** common in sexually active young adults and in children.
- It manifests as small papules (2 to 5 mm) with central umbilication. Lesions are asymptomatic. In HIV-positive patients, lesions can be

extensive (Figure 11-13).

- It is transmitted via skin-to-skin contact (sexual contact can lead to genital involvement) and is **highly contagious.**
- Often regresses spontaneously, but multiple treatment modalities are effective (e.g., curettage, drops containing podophyllin and cantharidin, cryosurgery), but scarring is always a risk.

***Quick* HIT**

Complications of Zoster

- Postherpetic neuralgia
- Occurs most frequently in patients older than 50 years
- Manifests as excruciating pain that persists after the lesions have cleared, and does not respond to analgesics
- Can be chronic and debilitating
- Uveitis
- Dissemination
- Meningoencephalitis, deafness

Herpes Zoster (Shingles)

A. General Characteristics

1. Caused by reactivation of the varicella-zoster virus, which remains dormant in the dorsal root ganglia and is reactivated in times of stress, infection, or illness; only occurs in those who have previously had chickenpox.
2. It is typically seen in patients over 50 years of age. In patients less than 50 years of age, suspect an immunosuppressed state.
3. Contagious when open vesicles present and only for those who have never had chickenpox or are immunocompromised (or newborns). Zoster is not as contagious as chickenpox.

B. Clinical Features

1. **Severe pain and rash in a dermatomal distribution.** Pain comes before the rash. Rash is characterized by grouped vesicles on an

erythematous base. If severe, low-grade fever and malaise may be present.

2. The most common sites of involvement are the thorax (most cases) and trigeminal distribution (especially ophthalmic division). Affected sites can also include other cranial nerves, as well as arms and legs (Figure 11-14).
3. Rarely life-threatening, even if dissemination occurs. Herpes zoster is more severe, however, in immunocompromised patients.

FIGURE 11-14 **Herpes zoster.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 6.33.)

C. Treatment

1. Keep the lesions clean and dry.
2. Prescribe analgesics for pain relief (acetaminophen or NSAIDs).

3. Prescribe antiviral agents (acyclovir, famciclovir, valacyclovir) to reduce the pain, decrease the length of illness, and reduce the risk of postherpetic neuralgia. Usually these must be started within the first 3 days of symptoms to be effective.
4. There is no convincing evidence for the routine use of steroids, gabapentin, or TCAs. For patients with severe pain for acute neuritis, these agents can be tried cautiously.
5. Vaccination is recommended for patients over the age of 60 (and for most patients over the age of 50, and even younger if immunosuppressed). The recombinant (nonlive) vaccine is the preferred vaccine.

Quick HIT

Treat tinea capitis and onychomycosis with oral antifungal agents. Others are treated with topical antifungals.

Dermatophytes

- Dermatophytes are superficial fungi that infect cutaneous epithelium, nails, and hair.
- The three main genera of dermatophytes are *Trichophyton, Microsporum,* and *Epidermophyton.*
- Important dermatophyte infections are covered in Table 11-1.
- Scrape lesions and use KOH preparation to visualize the fungus.

Tinea Versicolor

- A common superficial fungal infection which is likely caused by several species in the Malassezia group, which are part of the normal skin flora (Figure 11-15).
- Characteristic lesions are **well demarcated** and most commonly affect the trunk. As the name implies, lesions may be hyper- or hypopigmented and can range in color from brown to tan to white.
- Adolescents and young adults are most commonly affected, though almost any age can be affected.

- Hot/humid weather, excessive sweating, and skin oils may contribute to transformation from normal skin flora to pathologic condition.
- Diagnosis should be made with KOH prep, which will show the "spaghetti and meatballs" pattern consistent with both hyphae and yeast balls.
- Treatment consists of oral or topical antifungals, depending on the severity of the disease. Selenium sulfide lotion may also be helpful. Oral therapy is reserved for extensive involvement, or those who have failed oral treatment.

TABLE 11-1 Important Dermatophyte Infections

Fungal Infection	Location	Age Group	Findings	Diagnosis	First-Line Treatment
Tinea corporis ("ringworm")	Body/trunk	All ages	Pinkish, annular lesions	Direct microscopy: visualization of hyphae from skin scrapings with KOH preparation	Topical antifungals (e.g., ketoconazole, miconazole)
Tinea capitis	Scalp	Children	Areas of scaling with hair loss ± pruritus	• Direct microscopy • Wood lamp: if hairs fluoresce, *Microsporum* spp. is the cause. If not, *Trichophyton* spp. is the cause.	Oral griseofulvin or terbinafine
Tinea unguium (onychomycosis)	Nails	Elderly people	Thick, opacified nails	Direct microscopy (nail scrapings)	Oral terbinafine
Tinea pedis ("athlete's foot")	Feet—web spaces of toes	Young adults	Scaling, erythema, pruritus	Direct microscopy	Topical antifungals, good foot hygiene
Tinea cruris ("Jock itch")	Groin, inner thighs	Adults: males > females	Areas of scaling, erythema: spares scrotum	Direct microscopy	Topical antifungals, good hygiene

A 32-year-old woman presents with pruritic skin lesions on the upper back. The patient reports that the number of skin lesions has increased over the last 2 years. Physical examination reveals several hypopigmented macules of varying sizes affecting the upper back. Dermoscopy reveals fine scale over the majority of the lesions.

Which of the following is the correct treatment for this condition?

A. Topical corticosteroids
B. Terbinafine
C. Topical selenium sulfide
D. Reassurance

- **The answer is C: Topical selenium sulfide.** The patient in this question likely has pityriasis (tinea) versicolor, a superficial fungal infection with Malassezia species. The skin lesions in pityriasis versicolor are hypopigmented or hyperpigmented macules of varying sizes, often affecting the upper trunk, arms, chest, shoulders, and face. The skin lesions in this condition are often irregular, well demarcated, covered by a fine scale, and mildly pruritic. Given the interference with melanin production, pityriasis versicolor often results in hypopigmented lesions, but in light-skinned people, lesions can be pink or light brown. **(A)** Topical corticosteroids would treat the symptomatic itching, but not the underlying fungal infection. **(B)** Terbinafine would indeed treat pityriasis versicolor, but is too strong of a medication (associated hepatotoxicity) to use as first-line therapy. This would be an appropriate agent if the patient does not respond to topical treatment. **(D)** Reassurance should not be offered as a treatment option due to the pruritus affecting an individual's quality of life.

FIGURE 11-15 **Tinea versicolor.**
(Reprinted with permission from Gru AA, Wick MR, Mir A, et al. *Pediatric Dermatopathology and Dermatology*. Wolters Kluwer; 2018. Figure 20-1F.)

Scabies

A. General Characteristics

1. Caused by the human skin mite *Sarcoptes scabiei*.
2. Highly contagious—transmitted via skin-to-skin contact or through towels, bed linens, or clothes.
3. Pathogenesis—the mites tunnel into the epidermis, lay eggs, and deposit feces (called scybala). A delayed type IV hypersensitivity reaction develops toward the mites, eggs, and feces, causing intense pruritus.
4. Common locations include the fingers, interdigital areas, and wrists. In more extensive infestations, the elbows, feet, ankles, penis, scrotum,

buttocks, and axillae. The head, neck, palms, and soles are typically spared.

Quick HIT

Consider scabies in any patient who has persistent, generalized, severe pruritus.

B. Clinical Features

1. Severe pruritus—this is often the most severe during the night.
2. Burrows—linear marks (several millimeters in length) represent the tunneled path of the mite. There is typically a dark dot at one end, representing the female mite.
3. Scratching may lead to excoriations.
4. Eczematous plaques, crusted papules, or secondary bacterial infection may develop (Figure 11-16).

C. Diagnosis

1. Look for characteristic burrows on hands, wrists, and ankles, and in the genital region.
2. Confirm the diagnosis by scraping the burrow with a scalpel and examining it under a microscope to detect the presence of mites, ova, or scybala.

FIGURE 11-16 **Norwegian or crusted scabies.**
(Reprinted with permission from Goodheart HP, Gonzalez ME. *Goodheart's Same-Site Differential Diagnosis*. 2nd ed. Wolters Kluwer; 2022. Figure 14.27.)

D. Treatment

1. Specific medications.
   a. Permethrin 5% cream is often used as first-line treatment; it causes paralysis of the parasite (acts on nerve cell membrane).
      - Should be applied to **every area of the body** (head to toe), even under fingernails and toenails, around the genital area, and in the cleft of the buttocks. Patients should leave cream on overnight (>8 to 10 hours) and wash it off the next morning. Some recommend a second treatment 1 to 2 weeks later.

   b. Other options include oral ivermectin, topical lindane (γ-benzene-hexachloride), and others.
2. General recommendations.
   a. Treat all close contacts of the patient simultaneously (even if asymptomatic) with Permethrin 5% cream.
   b. The patient is no longer contagious after one treatment, although pruritus may continue for a few weeks as dead mites are shed from

the skin. Use topical corticosteroids and oral antihistamines to control pruritus during this time.
c. Thoroughly wash all underwear and bed linens.

BENIGN AND MALIGNANT SKIN LESIONS

Benign Skin Lesions

Actinic Keratosis (Also Called Solar Keratosis)

- Small, rough, scaly lesions due to prolonged and repeated sun exposure (Figure 11-17).
- Most commonly seen in fair-skinned people. Lesions are typically on the face.
- Prevention: advise patients to avoid excessive sun exposure and to use sunscreen.
- Although the risk of malignant transformation is low (1 in 1,000), biopsy is still recommended for hyperkeratotic actinic keratosis lesions to exclude SCC. In addition, lesions which become indurated, tender, or bleed spontaneously must be biopsied to exclude SCC.
- Treatment options include surgical removal (scraping), freezing with liquid nitrogen, or application of topical 5-FU for multiple lesions (destroys sun-damaged skin cells).

Quick HIT

Once a patient has developed actinic keratosis with excessive sun exposure, other lesions may develop, even without further sun exposure.

Seborrheic Keratosis

- These are very common skin lesions that begin to appear after the age of 30 years. They are benign and have a genetic predisposition.
- They are slightly elevated plaques, gradually turning darker in color, and appear as if they were "stuck" on the skin (Figure 11-18).
- Treatment is not necessary and is only for cosmetic reasons: liquid nitrogen cryotherapy or curettage is effective and easily performed in the office setting.

FIGURE 11-17 **Actinic keratosis.**
(Reprinted with permission from Stedman TL. *Stedman's Medical Dictionary for the Health Professions and Nursing: Illustrated*. 6th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2007.)

FIGURE
11-18 **Seborrheic keratosis.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 21.13.)

Keratoacanthoma

- Epithelial tumors which clinically resemble squamous cell carcinoma (SCC). Current debate centers on whether this is a subtype of SCC or a separate entity altogether.
- Lesions grow **VERY** quickly. The lesions progress to the typical dome with central crater containing keratinous material over the course of several weeks. This type of growth is very rare for SCC.
- Treatment involves observation, as many of these will regress spontaneously over several months.

A 62-year-old man with an insignificant past medical history presents with anxiety about several “skin bumps.” He has a family history of melanoma and endorses spending much time in the sun as a child. Physical examination is unremarkable except for a raised, hyperpigmented plaque (see Figure 11-18).

Which of the following represents the most appropriate next step in management?

A. Shave biopsy
B. Reassurance
C. Excisional biopsy
D. Topical corticosteroids

- **The answer is B: Reassurance.** The patient in this question is presenting with skin lesions that have a “stuck on” appearance with an overlying rough and scaly surface. This is a classic example of the common dermatologic condition known as seborrheic keratosis. Seborrheic keratoses are benign skin growths that require no treatment. **(A, C)** If there is doubt about the less common likelihood of nodular melanoma, a biopsy should be performed. Of note, the sudden appearance of many seborrheic keratoses can be a sign of a gastrointestinal malignancy.

Malignant Skin Lesions

Basal Cell Carcinoma

- **Basal cell carcinoma (BCC) is the most common skin cancer** (accounts for 60% to 75% of all skin cancers) and arises from the basal layer of cells in the epidermis.
- The most important risk factor is sun exposure.
- It occurs most frequently in fair-skinned individuals who burn easily and involves sun-exposed areas, such as the head and neck (the nose is the

most common site).

- The classic appearance is a pearly, smooth papule with rolled edges and surface telangiectasias (three Ps: pearly, pink, papule) (Figure 11-19).
- Metastasis is extremely rare, but can be locally destructive.
- Surgical resection is curative.

FIGURE 11-19 Basal cell carcinoma.
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 22.18.)

Quick HIT

Marjolin ulcer: an SCC arising from a chronic wound such as a previous burn scar (tends to be very aggressive)

Quick HIT

Women with malignant melanoma have a better prognosis than men (with equivalent lesions).

Squamous Cell Carcinoma

- SCC is less common than BCC (SCC accounts for less than 20% of all skin cancers) and arises from epidermal cells undergoing keratinization.
- Sunlight exposure is the most important risk factor. Concomitant actinic keratoses, chronic skin damage, and immunosuppressive therapy are also risk factors.
- It is typically described as a crusting, ulcerated nodule or erosion (Figure 11-20).
- The likelihood of metastasis is higher than with BCC, but much lower than with melanoma.
- The prognosis is excellent if it is completely excised (95% cure rate). Lymph node involvement, however, carries a poor prognosis.

Melanoma

A. General Characteristics

1. Most aggressive form of skin cancer and the number one cause of death due to skin cancer.
2. Increasing incidence worldwide
3. Risk factors
   a. Fair complexion; primarily affects Caucasian patients, especially those with any of the following:
      - Inability to tan
      - Easily sunburned
      - Red hair and/or freckles
      - Numerous moles

   b. Sun exposure, especially for:
      - Patients with a history of severe sunburn before the age of 14 years
      - Patients living in a sunny climate

c. Family history of melanoma (e.g., first-degree relative)
d. Genodermatoses (e.g., xeroderma pigmentosa)
e. Increasing age
f. Large numbers of nevi (moles)
   - Although most melanomas arise de novo, they may arise from pre-existing nevi in up to 50% of cases
   - Any change in a nevus is concerning because it may indicate malignancy or malignant transformation. Look for color change, bleeding, ulceration, or a papule arising from the center of an existing nevus
g. Dysplastic nevus syndrome
   - Numerous, atypical moles—these tend to be large with indistinct borders and variations in color. The chances of **a single** dysplastic nevus becoming a melanoma are small
   - If dysplastic nevus syndrome **and** a family history of melanoma are present, the risk of developing melanoma approaches 100%
h. Giant congenital nevi—the risk of melanoma is about 5% to 8%. Prophylactic excision is recommended

FIGURE 11-20 **Squamous cell carcinoma.**
(Reprinted with permission from Hall JC, Hall BJ. *Sauer's Manual of Skin Diseases*. 11th ed. Wolters Kluwer; 2017. Figure 31-18.)

***Quick* HIT**

Spitz Nevi

- Well-circumscribed, raised lesion commonly confused with melanoma; color varies.
- Complete excision is recommended.

4. Growth phases
   a. Radial (initial) growth phase
      - Growth is predominantly lateral within the epidermis
      - There is a good prognosis with surgical resection because metastasis is unlikely
   b. Vertical (later) phase
      - Growth extends into the reticular dermis or beyond

- Lymphatic or hematogenous metastasis may occur
- **Depth of invasion is the most important indicator of prognosis**

B. Clinical Features

1. A melanoma may present with some or all of the following features:
   a. Asymmetry
   b. Border irregularity
   c. Color variegation—ranging from pink to blue to black
   d. Diameter greater than 6 mm
   e. Evolution—changes in size, shape, or color (Figure 11-21)

FIGURE 11-21 **Malignant melanoma.**
(Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders: Diagnosis and Management*. 2nd ed. Lippincott Williams & Wilkins; 2003. Figure 21.20.)

C. Diagnosis

1. Excision biopsy is the standard of care for diagnosis of any suspicious lesion.
   a. Shave biopsy and punch biopsy are less accurate than excision biopsy in assessing the depth of invasion.
   b. Acceptable skin margins are 1 to 3 cm for most lesions, as determined by depth of invasion.

2. Lymph node dissection is appropriate if nodes are palpable.

***Quick* HIT**

Sites of Metastases

- Lymph nodes, skin, subcutaneous (59%)
- Lung (36%)
- Liver (20%)
- Brain (20%)—common cause of death
- Bone (17%)
- GI tract (7%)

D. Treatment

1. Early detection is the most important way to prevent death, because prognosis is directly related to depth of invasion.
2. Surgical options exist, and even surgical excision of metastases (termed metastasectomy) may be beneficial.
3. For advanced disease, immunotherapy or targeted therapies (e.g., BRAF inhibition) may be offered.

Ambulatory Medicine 12

Mark D. Duncan

Cardiovascular Diseases

Hypertension

A. General Characteristics

1. **Essential hypertension (HTN)** (i.e., there is no identifiable cause) **applies to more than 95% of cases of HTN**

Quick HIT

Birth control pills are the most common secondary cause of HTN in young women.

2. Secondary HTN has many identifiable causes
   a. **Renal/renovascular disease—renal artery stenosis (most common cause of secondary HTN)**, chronic renal failure, polycystic kidneys
   b. Endocrine causes—hyperaldosteronism, thyroid or parathyroid disease, Cushing syndrome, pheochromocytoma, acromegaly
   c. Medications—oral contraceptives, decongestants, estrogen, appetite suppressants, chronic steroids, tricyclic antidepressants (TCAs), nonsteroidal anti-inflammatory drugs (NSAIDs)
   d. Coarctation of the aorta
   e. Cocaine, other stimulants
   f. Obstructive sleep apnea (OSA)

Quick HIT

Pathophysiology of the Effects of HTN on the Heart

- Increased systemic vascular resistance (afterload) → concentric left ventricle hypertrophy (LVH) → decreased LV function. As a result, the chamber dilates → symptoms and signs of heart failure.
- HTN accelerates atherosclerosis, leading to a higher incidence of CAD (as well as peripheral vascular disease and stroke).

B. Risk Factors

1. Age—both systolic and diastolic BP increase with age
2. Gender—more common in men (gap narrows over age 60 years); men have higher complication rates
3. Race—it is twice as common in African-American patients than in Caucasian patients; African-American patients have higher complication rates (stroke, renal failure, heart disease)
4. Obesity, sedentary lifestyle, dyslipidemia
5. Family history
6. Increased sodium intake—this correlates with increased prevalence in large populations, but not in individuals; individual susceptibility to the effects of high salt intake varies
7. Alcohol—intake of more than 2 oz of liquor, 8 oz of wine, or 24 oz of beer per day is associated with HTN

Quick HIT

Target Organ Damage

- Heart—LVH, MI, CHF
- Brain—stroke, TIA
- Chronic kidney disease
- Peripheral arterial disease, AAA, aortic dissection
- Retinopathy

C. Definitions

1. **Classification (for adults >18 years)**
   a. **Normal—systolic BP <120 and diastolic BP <80**

b. **Elevated—systolic BP 120 to 129 or diastolic BP <80**
c. **Stage I—systolic BP 130–139 or diastolic BP 80–89**
d. **Stage II—systolic BP ≥140 or diastolic BP ≥90**

2. **Hypertensive urgency—severe HTN (typically systolic BP >180 and/or diastolic BP >120) in an asymptomatic patient**
3. **Hypertensive emergency—severe HTN with end-organ damage (e.g., neurologic changes, myocardial ischemia, aortic dissection)**
4. **White coat hypertension: elevated blood pressure when measured in the office setting, but not out of the office**
5. **Masked hypertension: elevated blood pressure outside the office, but does not meet criteria when measured in the office**

***Quick* HIT**

HTN is an asymptomatic disease ("silent killer")—it causes insidious damage to the following target organs: heart, eyes, CNS, and kidneys.

- **CHF is a common end-result of untreated HTN** as LVH occurs.
- Most deaths due to HTN are ultimately due to MI or CHF.
- HTN predisposes the patient to peripheral artery disease (PAD).
- HTN is associated with increased incidence of abdominal aortic aneurysm (AAA) and **aortic dissection.**

D. Complications

1. The major complications of HTN are cardiac complications (coronary artery disease [CAD], CHF with left ventricular hypertrophy [LVH]), stroke, and renal failure. These account for the majority of deaths associated with untreated HTN.
2. HTN affects the following organs (target organ damage):
   a. Cardiovascular system
      - Effects on the heart are most important. **HTN is a major risk factor for CAD,** with resultant angina and MI.

   b. Eyes (retinal changes)
      - Early changes—arteriovenous nicking (discontinuity in the retinal vein secondary to thickened arterial walls) and cotton wool spots (infarction of the nerve fiber layer in the retina) can cause visual disturbances and scotomata (Figure 12-1).
      - More serious disease—hemorrhages and exudates.

- **Papilledema**—an ominous finding seen with severely elevated BP.

c. CNS
- Increased incidence of **intracerebral hemorrhage.**
- Increased incidence of other stroke subtypes as well (transient ischemic attacks [TIAs], ischemic stroke, and lacunar stroke).
- Hypertensive encephalopathy when BP is severely elevated (uncommon).

d. Kidney
- Arteriosclerosis of afferent and efferent arterioles and glomerulus —called nephrosclerosis.
- Decreased GFR and dysfunction of tubules—with eventual **renal failure.**

Quick HIT

Patients with a systolic BP of 120 to 129 should be counseled about lifestyle modifications to prevent cardiovascular disease.

Quick HIT

Goals in Evaluating a Patient With HTN

- Look for secondary causes (may be treatable).
- Assess damage to target organs (heart, kidneys, eyes, CNS).
- Assess overall cardiovascular risk.
- Make therapeutic decisions based on the above.

Quick HIT

Definition of HTN

BP >130/80 in general population (including patients with diabetes and renal disease)

E. Diagnosis

1. BP measurement

a. Unless the patient has severe HTN or evidence of end-organ damage, never diagnose HTN on the basis of one BP reading. Establish the diagnosis on the basis of at least two readings over 4 or more weeks apart, ideally using home blood pressure monitoring in addition to office readings
b. Observe the following to obtain an accurate BP reading
   - The arm should be at heart level, and the patient should be seated comfortably
   - Have the patient sit quietly for at least 5 minutes before measuring BP
   - Make sure the patient has not ingested caffeine or smoked cigarettes in the past 30 minutes (both elevate BP temporarily)
   - Use a cuff of adequate size (a cuff that is too small can falsely elevate BP readings). The bladder within the cuff should encircle at least 80% of the arm

FIGURE 12-1 **Cotton wool spots (hypertension).**
(Reprinted with permission from Stoller JK, Ahmad M, Longworth DL. *The Cleveland Clinic Intensive Review of Internal Medicine*. 3rd ed. Lippincott Williams & Wilkins; 2002. Figure 6.1.)

2. Order the following laboratory tests to evaluate target organ damage and assess overall cardiovascular risk
   a. Urinalysis
   b. Chemistry panel: serum K^1, BUN, Cr
   c. Fasting glucose (if patient is diabetic, check for microalbuminuria)
   d. Lipid panel
   e. ECG
3. If the history and physical examination (H&P) or laboratory tests suggest a secondary cause of HTN, order appropriate tests

Quick HIT

Always obtain a pregnancy test in reproductive age women before starting an antihypertensive medication. Thiazides, ACE inhibitors, calcium channel blockers, and ARBs are contraindicated in pregnancy. β-Blockers and hydralazine are safe.

F. Treatment

1. Management goals.
2. Lifestyle changes, listed in order of effect on BP reduction:
   a. Weight loss lowers BP significantly. In patients with central obesity (who often have coexisting diabetes, hyperlipidemia, and other risk factors), weight loss is particularly important because multiple risk factors are reduced concomitantly.
   b. Follow a low–saturated-fat diet rich in fruits, vegetables, and low-fat dairy products (DASH diet).
   c. Exercise regularly. Regular aerobic exercise can lower BP (and reduce overall cardiovascular risk).
   d. Reduce salt intake. Reduction in dietary salt has been shown to reduce BP. Recommend either a no-added-salt diet (4 g sodium/day) or a low-sodium diet (2 g/day).
   e. Avoid excessive alcohol consumption. Alcohol has a pressor action, and excessive use can increase BP.
   f. Others—stop unnecessary medications that may contribute to HTN. Engage in appropriate stress management practices.
3. Pharmacologic treatment: typically a thiazide diuretic, calcium channel blocker, or ACE inhibitor/ARB is used as first line. Common adverse effects are listed in Table 12-1.
   a. Thiazide diuretics
      - Mechanism is as a diuretic by inhibiting NaCl reabsorption in the distal convoluted tubule. Chlorthalidone is often used as a first-line option, since it was studied in major trials such as ALLHAT.
      - A good option in patients with osteoporosis (increases calcium reabsorption in the nephron).
   b. β-Blockers—decrease HR and cardiac output and decrease renin release.

- A good option in patients with CHF, CAD, or atrial fibrillation; a poor option in patients with obstructive lung disease, heart block, or depression.

c. ACE inhibitors and ARBs
  - ACE inhibitors work by inhibiting the renin–angiotensin–aldosterone system (RAAS) by blocking the conversion of angiotensin I to angiotensin II. Angiotensin II normally causes vasoconstriction, aldosterone release, and ventricular remodeling. ARBs work by directly blocking angiotensin II receptors. See Figure 12-2.
  - ACE also acts to degrade bradykinin, so inhibition results in excess levels in the lung that can cause a chronic dry cough.
  - **Preferred in all diabetic patients** because of their protective effect on kidneys; also a good option for patients with CHF, CAD.
  - ACE inhibitors and ARBs should not be used in combination.

d. Calcium channel blockers—cause vasodilation of arteriolar vasculature

e. α-Blockers—decrease arteriolar resistance.
  - May be of benefit if the patient has concurrent benign prostatic hyperplasia (BPH) but these are not considered first- or second-line agents.

f. Vasodilators (hydralazine and minoxidil)—not commonly used; typically given in combination with β-blockers and diuretics to patients with refractory HTN.

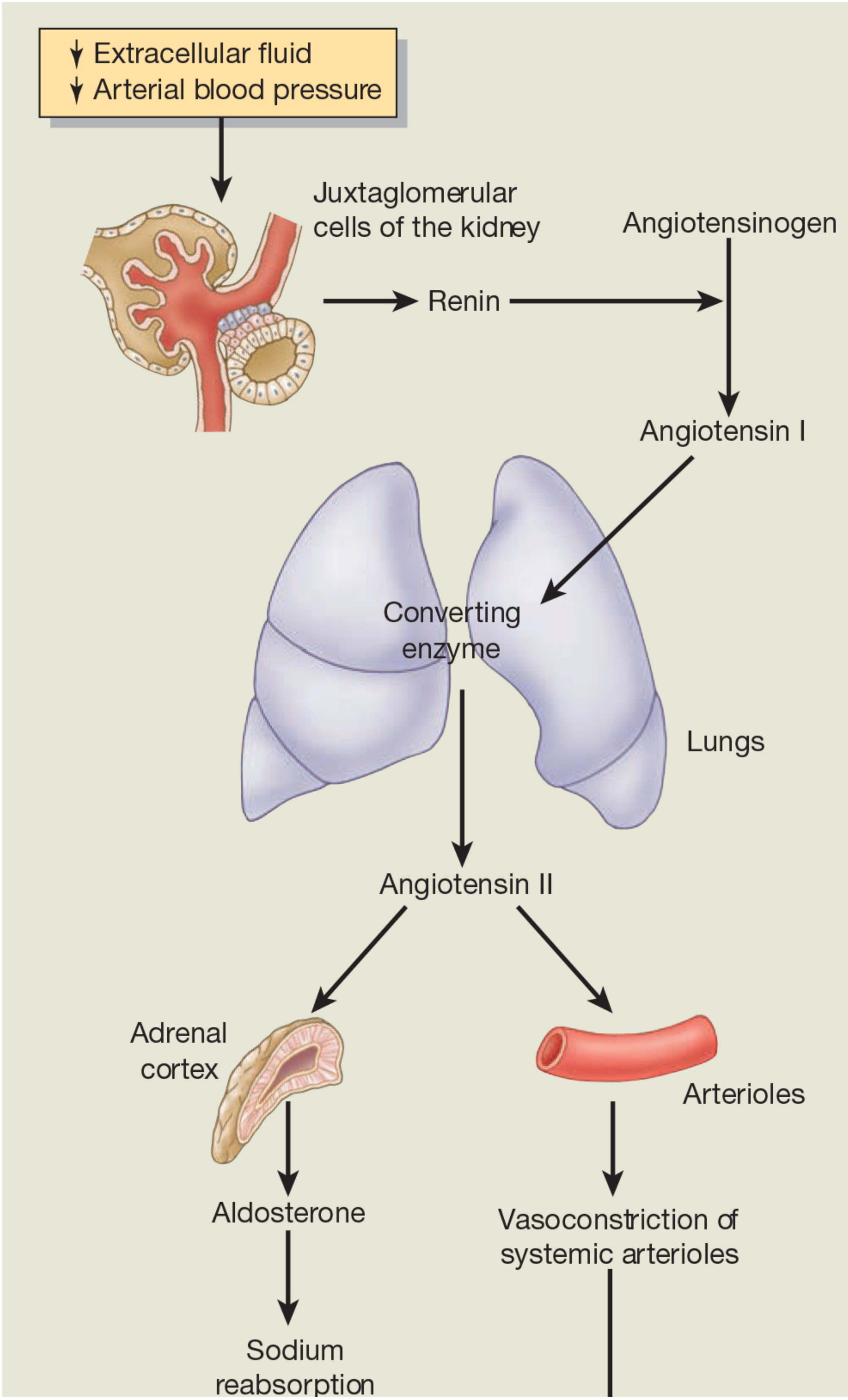
g. Mineralocorticoid receptor antagonist (e.g., spironolactone, eplerenone)—great option to add on in cases of resistant hypertension.

TABLE 12-1 Side Effects of Antihypertensive Medications

Medication	Side Effects
Thiazide diuretics	**Hypokalemia**, hyperuricemia, hyperglycemia, elevation of cholesterol and triglyceride levels, metabolic alkalosis, hypomagnesemia
β-Blockers	Bradycardia, bronchospasm, sleep disturbances (insomnia), fatigue, may increase TGs and decrease HDL, depression, sedation, may mask hypoglycemic symptoms in diabetic patients on insulin
ACE inhibitors	Acute renal failure, hyperkalemia, dry cough, angioedema, skin rash, altered sense of taste
Calcium channel blockers	Dihydropyridines (e.g., amlodipine): peripheral edema Nondihydropyridines (e.g., verapamil, diltiazem): heart block

Quick HIT

Unless there is a compelling indication to use a specific drug class, it makes little difference whether the initial drug is a thiazide diuretic, calcium channel blocker, or ACE inhibitor/ARB. However, since many patients will eventually require combination therapy, start with either a calcium channel blocker or ACE inhibitor/ARB so that the other can be added on later (this is a preferred combination).



↓ Extracellular fluid
↓ Arterial blood pressure
Juxtaglomerular cells of the kidney
Renin
Angiotensinogen
Angiotensin I
Converting enzyme
Lungs
Angiotensin II
Adrenal cortex
Arterioles
Aldosterone
Vasoconstriction of systemic arterioles
Sodium reabsorption

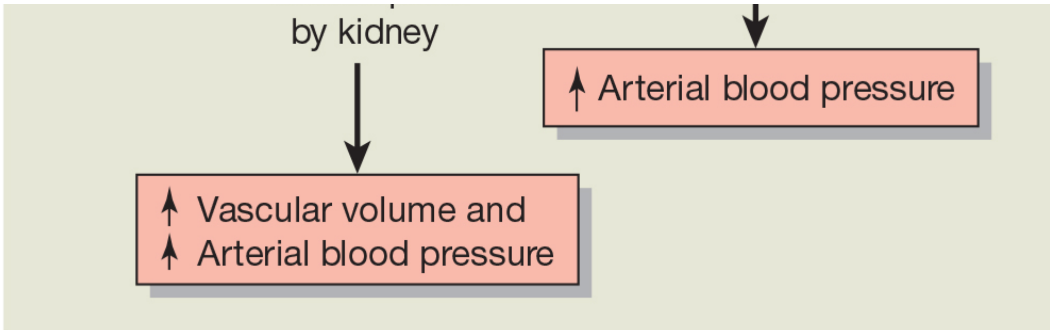


FIGURE 12-2 Control of blood pressure by the renin–angiotensin–aldosterone system.
(Reprinted with permission from Grossman S, Porth CM. *Porth's Pathophysiology: Concepts of Altered Health States*. 9th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013. Figure 31-4.)

Quick HIT

Treatment with ACE inhibitors and ARBs is associated with decreased risk of new-onset diabetes in patients with HTN.

Quick HIT

Most patients eventually need more than one drug to attain goal BP (especially diabetics, obese patients, and those with renal failure).

Quick HIT

Cardiovascular risk factors: smoking, diabetes, hypercholesterolemia, age over 60, family history, male sex (higher than for female only until menopause)

Clinical risk factors: presence of CAD, PAD, or prior MI; any manifestations of target organ disease—LVH, retinopathy, nephropathy; stroke or TIA

4. General principles of treatment
   a. Blood pressure targets should be based on the patient's cardiovascular risk, age, comorbidities such as postural hypotension,

etc.

b. The ACC/AHA guidelines recommend a BP goal of <130/80 mmHg for most patients, including older patients.
c. Each of the antihypertensive agents is roughly equally effective in lowering BP. However, there is great variability in how patients respond to each drug. The three classes of drugs that are used for initial monotherapy are thiazide diuretics, long-acting calcium channel blockers (most often a dihydropyridine), and ACE inhibitors/ARBs. β-Blockers are not commonly used as initial monotherapy in the absence of a specific indication because of adverse effects on some cardiovascular outcomes especially in elderly patients.
d. Drug treatment is often lifelong. However, patients with very mild HTN may be able to be weaned off medication if their BP can be lowered and controlled with nonpharmacologic measures, such as lifestyle modifications. However, these patients need frequent BP checks.
e. ALLHAT trial compared chlorthalidone, amlodipine, lisinopril, and doxazosin in patients with essential HTN and at least one CAD risk factor. The doxazosin arm was terminated early because of an increased risk of CHF compared to chlorthalidone. The other three agents were similar in regard to rates of fatal CAD and nonfatal MI, however chlorthalidone reduced rates of CAD, stroke, CHF, and angina when compared to lisinopril.
f. ACCOMPLISH trial showed that treatment with antihypertensive combination therapy—the ACE inhibitor benazepril plus the calcium channel blocker amlodipine—was more effective than treatment with the ACE inhibitor plus diuretic. Based on this trial, it is common practice to start monotherapy with either a calcium channel blocker or an ACE inhibitor, so that the other can be added if combination therapy is needed.
g. If the patient's response to one agent is not adequate, there are two options:
    - Increase the dose of the first agent to the maximum dose.
    - Add a second medication (thiazide, calcium channel blocker, ACE inhibitor, or ARB); if target BP not achieved, increase the dose of each as necessary until the maximum dose is achieved.

h. If a patient's response is still inadequate with two agents, consider a third agent and referral to an HTN specialist.

i. The decision of when to start pharmacologic treatment is based on the patient's total cardiovascular risk, not just the elevation in BP.

- For any level of BP elevation, the presence of cardiovascular risk factors and/or comorbid conditions dramatically accelerates the risk from HTN, and therefore modifies the treatment plan. Estimation of overall risk depends on **cardiovascular risk factors** and **clinical risk factors** (see Clinical Pearl 12-1).

Hyperlipidemias

A. General Characteristics

1. Hyperlipidemia is one of the most important (and modifiable) risk factors for CAD. It causes accelerated atherosclerosis
2. Hyperlipidemia may be a primary disorder, such as a familial dyslipidemia syndrome, or secondary to another cause
3. Classification of dyslipidemia syndromes—types IIA, IIB, and IV account for over 80% of all of familial dyslipidemias (Table 12-2)

CLINICAL PEARL 12-1

Risk Factors for CAD in Evaluation of Patients With Hyperlipidemia

- Current cigarette smoking (dose-dependent risk)
- HTN
- Diabetes mellitus
- Low HDL cholesterol (<35 mg/dL); high HDL (>60 mg/dL) is a negative risk factor (subtract 1 from total)
- Age
  - Male: >45 years of age
  - Female: >55 years of age
- Male gender—if you count as a risk factor, do not count age
- Family history of premature CAD
  - MI/sudden death in male first-degree relative <55 years of age
  - MI/sudden death in female first-degree relative <65 years of age

4. Secondary causes of hyperlipidemia
   a. Endocrine disorders—hypothyroidism, DM, Cushing syndrome
   b. Renal disorders—nephrotic syndrome, uremia
   c. Chronic liver disease
   d. Medications—glucocorticoids, estrogen, thiazide diuretics, β-blockers
   e. Pregnancy
5. Risk factors
   a. Diet
      - Saturated fatty acids and cholesterol cause elevation in LDL and total cholesterol
      - High-calorie diets do not increase LDL or cholesterol levels (are “neutral”) but do increase triglyceride (TG) levels
      - Alcohol increases TG levels and HDL levels but does not affect total cholesterol levels
   b. Age—cholesterol levels increase with age until approximately age 65 years. The increase is greatest during early adulthood—about 2 mg/dL per year
   c. Inactive lifestyle, abdominal obesity
   d. Family history of hyperlipidemia

e. Gender—men generally have higher cholesterol levels than women; when women reach menopause, cholesterol levels then equalize and may even be higher in women than in men

f. Medications
- Thiazides—increase LDL, total cholesterol, TG (VLDL) levels
- β-Blockers (propranolol)—increase TGs (VLDL) and lower HDL levels
- Estrogens—TG levels may be further increased in patients with hypertriglyceridemia
- Corticosteroids and HIV protease inhibitors can elevate serum lipids

g. Genetic mutations that predispose to the most severe hyperlipidemias

h. Secondary causes of dyslipidemia (see above)

TABLE 12-2 Dyslipidemia Syndromes

Class	Name	Lipoprotein Elevated	Treatment
Type I	Exogenous hyperlipidemia	Chylomicrons	Diet
Type IIa	Familial hypercholesterolemia	LDL	Statins Niacin Cholestyramine
Type IIb	Combined hyperlipoproteinemia	LDL + VLDL	Statins Niacin Gemfibrozil
Type III	Familial dysbetalipoproteinemia	IDL	Gemfibrozil Niacin
Type IV	Endogenous hyperlipidemia	VLDL	Niacin Gemfibrozil Statins
Type V	Familial hypertriglyceridemia	VLDL + chylomicrons	Niacin Gemfibrozil

IDL, intermediate density lipoprotein.

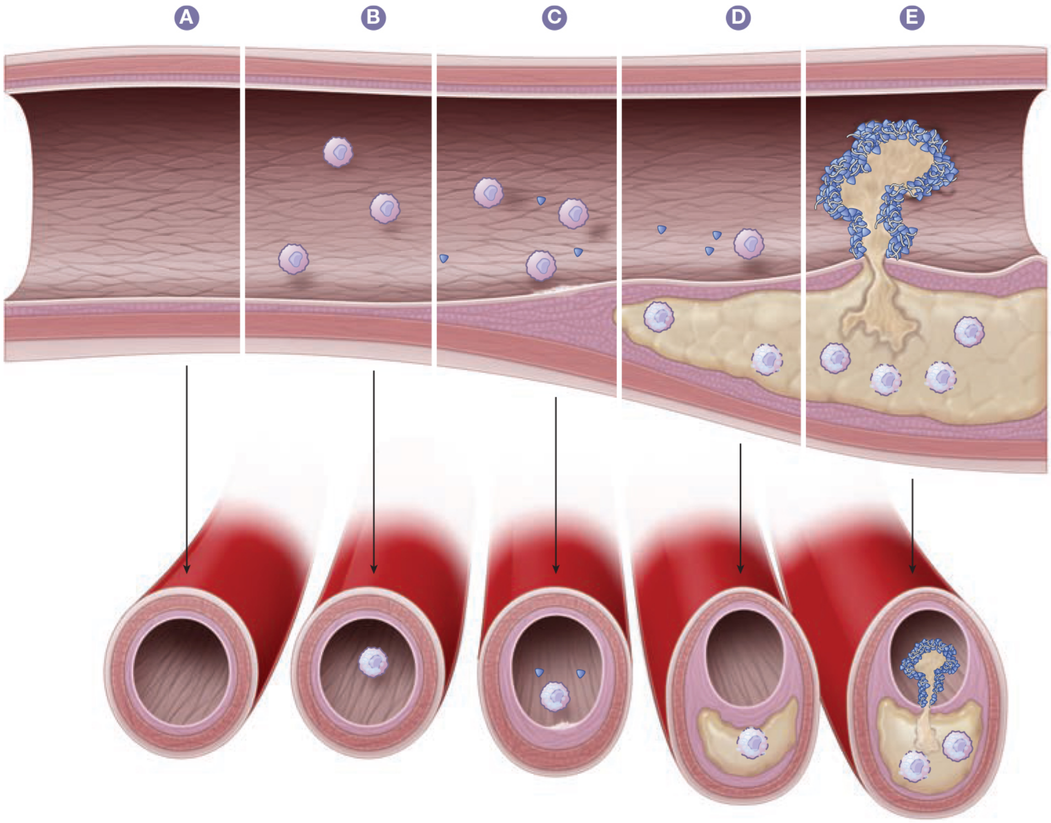


FIGURE 12-3 Progression of atherosclerotic plaque formation and rupture.
(Reprinted with permission from Golan DE, Tashjian AH, Armstrong EJ, et al. *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*. 3rd ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. Figure 25-7.)

6. Role of lipids in CAD risk

a. LDL cholesterol

- Accounts for two-thirds of total cholesterol. **CAD risk is primarily due to the LDL component** because LDL is the most atherogenic of all lipoproteins (Figure 12-3).
- LDL cholesterol is not directly measured. It is calculated as follows: LDL = total cholesterol − HDL − TG/5

b. Total cholesterol

- The risk of CAD increases sharply when total cholesterol is above 240 mg/dL

c. HDL cholesterol

- Its protective effect (removes excess cholesterol from arterial walls) is at least as strong as the atherogenic effect of LDL
- For every 10 mg/dL increase in HDL levels, CAD risk decreases by 50%
- High HDL (>60 mg/dL) is a "negative" risk factor (counteracts one risk factor) for CAD

d. **The total cholesterol-to-HDL ratio**—the lower the total cholesterol-to-HDL ratio, the lower the risk of CAD
- Ratio of 5.0 is average (standard) risk
- Ratio of 10 is double the risk
- Ratio of 20 is triple the risk
- Ratio of <4.5 is desirable

e. TGs—elevated TGs are associated with coronary risk, but it is unknown whether this association is causal. It is uncertain whether lowering TG level reduces coronary risk.

Quick HIT

Estrogen Replacement Therapy in Postmenopausal Women

The HERS trial showed no benefit of hormone replacement therapy on cardiovascular outcomes in women with established CHD. However, the study did not address the issue in women without CHD. The results are somewhat controversial.

A 49-year-old man presents for routine physical examination. The patient has no active complaints today other than occasional constipation and increased frequency of urination. The patient reports that he has a diagnosis of “pre-diabetes” given to him by his previous physician in another city. His family history is significant for hypertension. The patient denies alcohol use but smokes ½ pack of cigarettes daily. He works as a long-distance truck driver. Physical examination is unremarkable except for a body mass index of 31 kg/m^2. The patient’s fasting laboratory values reveal the following.

Hemoglobin A1c	7.9%
Serum glucose	170 mg/dL
Total cholesterol	220 mg/dL
Low-density lipoprotein (LDL)	145 mg/dL
Triglycerides	130 mg/dL
High-density lipoprotein	38 mg/dL

Which of the following is the best next step in the management of this patient?

A. Lifestyle modification
B. Atorvastatin and lifestyle modification
C. Sulfonylurea
D. Niacin, fish oil, and lifestyle modification

- **The answer is B: Atorvastatin and lifestyle modification.** This patient is presenting with a new diagnosis of diabetes mellitus (T2DM) based on his hemoglobin A1c. Patients with diabetes are at significant risk for cardiovascular atherosclerotic events. Based on his risk factors and lipid screen, he is at an elevated risk (>10%) of cardiovascular events and should begin statin therapy. Risk score calculators are available for this purpose. **(C)** A sulfonylurea (e.g.,

glimepiride) is not the initial drug of choice with new-onset diabetes. Metformin therapy is recommended after diagnosing T2DM. **(D)** Niacin is helpful in raising high-density lipoprotein, but may actually worsen glucose control in diabetics. Fish oil is helpful in reducing serum triglycerides but does not have an effect on improving cardiovascular outcomes.

B. Clinical Features

1. Most patients are asymptomatic
2. The following may be manifestations of severe hyperlipidemia:
   a. *Xanthelasma*—yellow plaques on eyelids.
   b. *Xanthoma*—hard, yellowish masses found on tendons (finger extensors, Achilles tendon, plantar tendons)
3. Pancreatitis can occur with severe hypertriglyceridemia

Quick HIT

Statins have been shown to significantly reduce rates of MI, stroke, and coronary and all-cause mortality in prospective placebo-controlled trials.

C. Diagnosis

1. Lipid screening (see Health Maintenance section)—measure total cholesterol and HDL levels (nonfasting is acceptable). If either is abnormal, then order a full fasting lipid profile
2. A full fasting lipid profile includes TG levels and calculation of LDL levels
3. Consider checking laboratory tests to exclude secondary causes of hyperlipidemia
   a. TSH (hypothyroidism)
   b. LFTs (chronic liver disease)
   c. BUN and Cr, urinary proteins (nephrotic syndrome)
   d. Glucose levels (diabetes)

D. Treatment

1. Recent pharmaceutical advances and guidelines (including ACC/AHA) have dramatically changed the treatment of dyslipidemias in the last decade. See Table 12-3.
   a. The long-term goal is the same: to reduce morbidity and mortality from CAD by promoting a healthy diet and lifestyle throughout life.
   b. Statins are still the first-line treatment for patients with atherosclerotic cardiovascular disease (ASCVD) or at high risk. Indications for starting a statin include established ASCVD, LDL levels of 190 mg/dL or higher, diabetic patients aged 40 to 75 years with LDL level of 70 mg/dL or higher, or all patients aged 40 to 75 years with ASCVD risk of at least 7.5% or higher (using the ACC/AHA ASCVD risk calculator).
   c. If LDL remains >100 mg/dL despite statin therapy, consider adding ezetimibe.
   d. If LDL remains >100 mg/dL despite statin + ezetimibe, consider adding a PCSK9 inhibitor (e.g., evolocumab, alirocumab). This can be considered also in the case of statin intolerance.
   e. Dietary therapy is important before and during statin therapy. Lowering fat intake (especially saturated fats) reduces serum cholesterol more than lowering cholesterol intake. Foods rich in omega-3 fatty acids (such as fish) are particularly beneficial. With an intensive diet, LDL can be reduced by an average of 10%, as follows: <30% of total calories from fat; with fewer than 10% from saturated fat; <300 mg/day of cholesterol.
   f. Exercise and weight loss—reduce risk of CAD.
      - Exercise increases HDL and reduces other CAD risk factors by lowering BP and enhancing the efficiency of peripheral oxygen extraction.
      - Weight loss reduces myocardial work as well as the risk of diabetes.
   g. Smoking cessation

TABLE 12-3 Updated Cholesterol Treatment Guidelines

Cholesterol Treatment to Reduce Cardiovascular Events	
Category	**Recommended Therapy**
Clinical ASCVD[a]	High-intensity statin. Can add ezetimibe if LDL still above 70 mg/dL after statin. Can add PCSK9 inhibitor if still above 70 m/dL.
LDL cholesterol ≥190 mg/dL	High-intensity statin for ages 20–75 yrs. Can add ezetimibe if LDL reduction not at least 50%, or still above 100 mg/dL. Consider bile acid sequestrant if TGs >300 mg/dL. PCSK9 inhibitors can be considered if above goals not met.
Diabetic patients aged 40–75 yrs	Moderate-intensity statin for all patients, high-intensity statin for those with ASCVD risk factors. If ASCVD score >20% can consider adding ezetimibe.
Nondiabetic patients aged 40–75 yrs with LDL cholesterol 70–189 mg/dL	ASCVD risk score ≥7.5%, consider moderate-intensity statin. If >20%, then start a high-intensity statin.

[a]ASCVD, atherosclerotic cardiovascular disease, which includes patients with acute coronary syndromes or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease from atherosclerosis.

Modified from Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;73(24):e285--e350.

Quick HIT

Potency of HMG CoA reductase inhibitors (“statins”):

- High intensity: atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg
- Moderate intensity: atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin 20 to 40 mg, lovastatin 40 to 80 mg, pravastatin 40 to 80 mg, fluvastatin XL 80 mg (or 40 mg twice daily), pitavastatin 1 to 4 mg
- Low intensity: simvastatin 10 mg, pravastatin 10 to 20 mg, lovastatin 20 mg, fluvastatin 20 to 40 mg

Quick HIT

It is no longer recommended to routinely monitor AST and ALT after starting a statin.

A 39-year-old man presents for his annual physical examination. He has a history of asthma, pre-hypertension, and Gilbert syndrome. The patient smokes a pack of cigarettes per day, but is pleased because he has cut it down from 2.5 packs per day. He has smoked since the age of 20 years. The patient is motivated at this visit to seek assistance in smoking cessation.

Which of the following medications can help him quit smoking in both the short and long term?

A. Propranolol
B. Buspirone
C. Bupropion
D. Paroxetine

- **The answer is C: Bupropion.** Bupropion is a drug primarily used as an atypical antidepressant and is used in smoking cessation. Though varenicline is not listed, it is another agent used for smoking cessation that likely even more effective than bupropion. Varenicline acts via partial agonism of nicotinic acetylcholine receptors. Nicotine-replacement therapy, either alone or in addition to bupropion or varenicline, can also be used and may be more effective than using either medication alone. Bupropion is unique compared to the other antidepressant drugs in that it has no sexual side effects. It should not be used in bulimic patients and those at risk of seizures because it can lower the seizure threshold.

2. Therapy for high TG levels—the data are fairly limited regarding which patients should be treated and which medication to use.

a. First-line therapy is weight loss, aerobic exercise, glycemic control in diabetics, and low-fat diet. Typically patients will be on a medication to lower LDL levels (e.g., statin), which will also help lower TG levels. However, if TG levels remain elevated, additional medications can be considered. This decision is typically based on ASCVD risk factors, history of pancreatitis from hypertriglyceridemia, etc.
b. Medications include icosapent ethyl, fibrates, nicotinic acid (niacin), and fish oil.

***Quick* HIT**

Emergency Evaluation of Headache

- Obtain a noncontrast CT scan to first rule out any type of intracranial bleed.
- However, small bleeds (subarachnoid hemorrhage) may be missed by CT scan, so a lumbar puncture may be necessary (to potentially visualize the presence of blood breakdown products).

Headache

Tension Headache

A. General Characteristics

1. Cause is unknown; may be similar to that of migraines (see below) (see also Clinical Pearls 12-2 and 12-3)
2. Usually worsens throughout the day; precipitants include anxiety, depression, and stress
3. Mild migraines can easily be confused with tension headaches and vice versa

B. Clinical Features

1. Pain is steady, aching, “vise-like,” and encircles the entire head (tight band-like pain around the head).

a. Usually generalized, but may be the most intense around the neck or back of head.
b. Can be accompanied by tender muscles (posterior cervical, temporal, frontal).
c. Tightness in posterior neck muscles.

C. Treatment

1. Attempt to find the causal factor(s). Evaluate the patient for possible depression or anxiety. Stress reduction is important.
2. NSAIDs (such as aspirin) and acetaminophen are the standard treatment for mild/moderate headaches.
3. If headaches are severe, medications that are used for migraines (triptans) may be appropriate, given the difficulty in distinguishing between these two entities.

CLINICAL PEARL 12-2

Differential Diagnosis of Headache

- Primary headache syndromes—migraines, cluster headache, tension headache
- Secondary causes of headache ("VOMIT")
  - **V**ascular—subarachnoid hemorrhage, subdural hematoma, epidural hematoma, intraparenchymal hemorrhage, temporal arteritis
  - **O**ther causes—malignant HTN, pseudomotor cerebri, postlumbar puncture, pheochromocytoma
  - **M**edication/drug related—nitrates, alcohol withdrawal, chronic analgesic use/abuse
  - **I**nfection—meningitis, encephalitis, cerebral abscess, sinusitis, herpes zoster, fever
  - **T**umor

CLINICAL PEARL 12-3

Headache Red Flags

- Sudden onset within seconds to minutes.
- Worst headache of the patient's life.
- New-onset headache that the patient has never experienced before, especially over the age of 50 years.
- Headache pattern: increase in severity and frequency over time, worse after lying down.
- Mental status change or any focal neurologic symptoms/signs.
- New-onset headache associated with heavy exertion or head trauma.
- New-onset headache associated with fever, stiff neck, or rash.
- New-onset headache in a patient with HIV infection or cancer.

Cluster Headaches

A. General Characteristics

1. Very rare—thought by some to be a variant of migraine headache
2. Usually occurs in middle-aged men
3. Subtypes
   a. Episodic cluster headaches (90% of all cases)—last 2 to 3 months, with remissions of months to years
   b. Chronic cluster headaches (10% of all cases)—last 1 to 2 years; headaches do not remit

B. Clinical Features

1. Excruciating periorbital pain ("behind the eye")—**almost always unilateral**
2. Cluster headache is described as a "deep, burning, searing, or stabbing pain." Pain may be so severe that the patient may even become suicidal
3. Accompanied by ipsilateral lacrimation, facial flushing, nasal stuffiness/discharge
4. Usually begins a few hours after the patient goes to bed and lasts for 30 to 90 minutes; awakens patient from sleep (but daytime cluster

headaches can also occur)
5. Attacks occur nightly for 2 to 3 months and then disappear. Remissions may last from several months to several years
6. Worse with alcohol and sleep

C. Treatment

1. Acute attacks
   a. **Sumatriptan** (Imitrex) and inhaled O_2 are the first-line treatments
2. Prophylaxis
   a. Of all the headache types, cluster headaches are the most responsive to prophylactic treatment. Offer all patients prophylactic medication. **Verapamil** taken daily is the drug of choice
   b. Ergotamine, methysergide, lithium, and corticosteroids (prednisone) are alternative agents
   c. These agents cause resolution (or marked reduction) of the number of headaches within 1 week

Quick HIT

Visual Aura in Migraine

- The classic presentation is a bilateral homonymous scotoma. Bright, flashing, crescent-shaped images with jagged edges often appear on a page, obscuring the underlying print. The aura usually lasts 10 to 20 minutes.
- A patient may have isolated visual migraines (as above) without headaches.

Migraine

A. General Characteristics

1. An inherited disorder (probably an autosomal dominant trait with incomplete penetrance)
2. The pathogenesis is not clearly defined, but serotonin depletion plays a major role

3. More common in women than men; more common in those with a family history; typically occurs one to two times per month
4. Types
   a. Migraine with aura (15% of cases)—"classic migraine." Aura is usually visual (flashing lights, scotomata, visual distortions), but can be neurologic (sensory disturbances, hemiparesis, dysphasia)
   b. Migraine without aura (85% of cases)—"common migraine"
   c. Menstrual migraine
      - Occurs between 2 days before menstruation and the last day of menses; linked to estrogen withdrawal
      - Treatment is similar to that of nonmenstrual migraine except that estrogen supplementation is sometimes added
   d. Status migrainosus—lasts over 72 hours and does not resolve spontaneously
5. The following can provoke a migraine:
   a. Hormonal alteration (menstruation)
   b. Stress, anxiety
   c. Sleeping disturbances (lack of sleep)
   d. Certain drugs/foods—chocolate, cheese, alcohol, smoking, oral contraceptive pills
   e. Weather changes and other environmental factors

Quick HIT

Many patients who are labeled as having migraines actually have **rebound analgesic headaches.** These occur more frequently (every 1 to 2 days) than migraines. These headaches do not respond to drugs used to treat migraines. Wean patient from analgesics. Do not use narcotics!

B. Clinical Features

1. Prodromal phase (occurs in 30% of patients)
   a. Consists of symptoms of excitation or inhibition of the CNS: elation, excitability, increased appetite and craving for certain foods (especially sweets); alternatively, depression, irritability, sleepiness, and fatigue may be manifested
   b. May precede the actual migraine attack by up to 24 hours

2. Severe, throbbing, unilateral headache (not always on the same side)
   a. Lasts 4 to 72 hours
   b. At times, it may be generalized over the entire head and may last for days if not treated
   c. Pain is aggravated by coughing, physical activity, or bending down
   d. Variable pain quality—“throbbing” or “dull and achy”
3. Other symptoms include nausea and vomiting (in as many as 90% of cases), photophobia, and increased sensitivity to smell

Quick HIT

Most patients experience a decrease in the number and intensity of headaches as they age.

C. Treatment

1. Acute attacks of migraine
   a. If migraines are mild, analgesics such as NSAIDs or acetaminophen may be effective. If they are not effective, a combination of an NSAID with a triptan is usually effective.
   b. DHE—a serotonin (5-HT1) receptor agonist
      - This is highly effective in terminating migraine pain. It is available for SC, IM, IV, or nasal administration
      - Contraindications—CAD, pregnancy, TIAs, PAD, sepsis
   c. Sumatriptan—a more selective 5-HT1 receptor agonist than DHE or other triptans
      - Acts rapidly (within 1 hour) and is highly effective
      - Should not be used more than once or twice per week
      - Contraindications—CAD, pregnancy, uncontrolled HTN, basilar artery migraine, hemiplegic migraine, use of MAOI, SSRI, or lithium
   d. Calcitonin-gene related peptide (CGRP) antagonists, such as rimegepant and ubrogepant, can be used for an acute attack.
   e. Lasmiditan is also effective for a migraine attack, and works by blocking the serotonin 1F receptor.
   f. Valproic acid may also be effective in resistant cases.

g. Additional adjunctive agents include antiemetics (e.g., metoclopramide or prochlorperazine), diphenhydramine (prevents akathisias with IV antiemetics), steroids (prevents early rebound).

2. Prophylaxis (must be taken daily)
   a. Consider prophylaxis for patients with weekly episodes that are interfering with activities. Before initiating prophylactic medications, the patient should make attempts to avoid any known precipitants of the migraines
   b. First-line agents include amitriptyline (TCAs) and propranolol (β-blocker). Propranolol is most effective of the prophylactic medications for migraines
   c. Second-line agents include verapamil (calcium channel blocker), valproic acid (anticonvulsant), and methysergide
   d. NSAIDs are effective for menstrual migraines

Upper Respiratory Diseases

Cough

A. General Characteristics

1. Cough can be divided into acute (less than 3 weeks duration) and chronic (more than 3 weeks duration)
2. If the cause is benign, cough usually resolves in a few weeks. If a cough lasts for longer than 1 month, further investigation is warranted

Quick HIT

Postnasal Drip

The mucosal receptors in the pharynx and larynx are stimulated by secretions of the nose and sinuses that drain into the hypopharynx.

3. Causes

a. Conditions that are usually associated with other symptoms and signs
   - Upper respiratory infections (URIs)—this is probably the most common cause of acute cough
   - Pulmonary disease—pneumonia, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, lung cancer, asthma, lung abscess, tuberculosis
   - CHF with pulmonary edema

b. Isolated cough in patients with normal chest radiograph
   - Smoking
   - Postnasal drip—may be caused by URIs (viral infections), rhinitis (allergic or nonallergic), chronic sinusitis, or airborne irritants
   - Gastroesophageal reflux disease (GERD)—especially if nocturnal cough (when lying flat, reflux worsens due to position and decreased lower esophageal sphincter [LES] tone)
   - Asthma—cough may be the only symptom in 5% of cases
   - ACE inhibitors—may cause a dry cough (by inhibiting bradykinin breakdown, leading to increased bradykinin production)

Quick HIT

Causes of Chronic Cough in Adults

- **Smoking**
- Postnasal drip
- GERD
- Asthma

B. Diagnosis

1. Usually no tests are indicated in a patient with acute cough.
2. CXR is indicated only if a pulmonary cause is suspected, if the patient has hemoptysis, or if the patient has a chronic cough. It also may be appropriate in a long-term smoker in whom COPD or lung cancer is a possibility.
3. CBC if infection is suspected.
4. Pulmonary function testing if asthma is suspected or if cause is unclear in a patient with chronic cough.

5. Bronchoscopy (if there is no diagnosis after above workup) to look for tumor, foreign body, or tracheal web.

C. Treatment

1. Treat the underlying cause, if known
2. Smoking cessation, if smoking is the cause
3. Postnasal drip—treat this with a first-generation antihistamine/decongestant preparation. If sinusitis is also present, consider antibiotics. For allergic rhinitis, consider a nonsedating long-acting oral antihistamine (loratadine)
4. Nonspecific antitussive treatment
   a. Unnecessary in most cases, because cough usually resolves with specific treatment of the cause
   b. May be helpful in the following situations:
      - If cause is unknown (and thus specific therapy cannot be given)
      - If specific therapy is not effective
      - If cough serves no useful purpose, such as clearing excessive sputum production or secretions
   c. Medications
      - Codeine
      - Dextromethorphan
      - Benzonatate (Tessalon Perles) capsules
   d. Agents used to improve the effectiveness of antitussive medications include expectorants such as guaifenesin and water

A 24-year-old female presents to her urgent care with 5 days of chills, malaise, and cough. She states her phlegm has now become more yellow and green, and she is requesting an antibiotic since she has a history of pneumonia. Vital signs are normal, and she has bilateral rhonchi on examination.

Which of the following is the best next step?

A. Start azithromycin
B. Start oseltamivir
C. Send sputum for gram stain and culture
D. Symptomatic treatment

- **The answer is D: Symptomatic treatment.** This is a common presentation at urgent care centers. The normal vitals and examination are reassuring, and this patient likely has a viral infection. (**A**) Thus, antibiotics are inappropriate at this time. (**B**) Unless there is a positive influenza test or the patient is at risk for complications from influenza, empiric oseltamivir is not necessary. (**C**) Testing the sputum is unlikely to be helpful, and is not recommended.

Acute Bronchitis

A. General Characteristics

1. Viruses account for the majority of cases.
2. Laboratory tests are not indicated. Obtain a chest radiograph only if you suspect pneumonia; there is no infiltrate or consolidation in acute bronchitis (presence of fever, tachypnea, crackles, egophony on auscultation, or dullness to percussion suggests pneumonia).

B. Clinical Features

1. **Cough (with or without sputum) is the predominant symptom**—it lasts 1 to 2 weeks. In a significant number of patients, the cough may

last for 1 month or longer.
2. Chest discomfort and shortness of breath may be present.
3. Fever may or may not be present.

C. Treatment

1. Antibiotics are usually **not** necessary—most cases are viral.
2. Cough suppressants (codeine-containing cough medications) are effective for symptomatic relief.
3. Bronchodilators (albuterol) may relieve symptoms.

The Common Cold

A. General Characteristics

1. The "common cold" is the most common upper respiratory tract infection. Children are more frequently affected than adults. Susceptibility depends on pre-existing antibody levels.
2. Caused by viruses (identification of virus is not important).
   a. Rhinoviruses are the most common (at least 50% of cases)—there are more than 100 antigenic serotypes, so reinfection with another serotype can lead to symptoms (no cross-immunity among the serotypes).
   b. Other viruses include coronavirus, parainfluenza viruses (types A, B, and C), adenovirus, coxsackievirus, and RSV.
3. **Hand-to-hand transmission** is the most common route.
4. Complications include secondary bacterial infection (bacterial sinusitis or pneumonia). These secondary infections (especially pneumonia) are very rare.
5. Most resolve within 1 week, but symptoms may last up to 10 to 14 days.

Quick HIT

- The common cold is synonymous with acute rhinosinusitis—inflammation and congestion of mucous membranes of nasal and sinus passages.
- In most cases, it is very difficult to distinguish between the common cold (viral rhinosinusitis) and acute bacterial sinusitis on the basis of clinical features.
- Sneezing/rhinorrhea, nasal discharge (whether clear, purulent, or colored), nasal obstruction, and facial pain/headaches occur in both.

B. Clinical Features

1. Rhinorrhea, sore throat, malaise, nonproductive cough, nasal congestion.
2. Fever is uncommon in adults (suggests a bacterial complication or influenza), but is not unusual in children.

Quick HIT

Many of the symptoms seen with the common cold are also seen in influenza, but are more severe in the latter. Fever, headache, myalgias, and malaise are much more pronounced with influenza.

C. Treatment (Symptomatic)

1. Adequate hydration
   a. Loosens secretions and prevents airway obstruction
   b. Can be achieved by increasing fluid intake and inhaling steam
2. Rest and analgesics (aspirin, acetaminophen, ibuprofen)—for relief of malaise, headache, fever, aches
3. Cough suppressant (dextromethorphan, codeine)
4. Nasal decongestant spray (Neo-Synephrine) for less than 3 days
5. Oral first-generation antihistamines for rhinorrhea/sneezing

Sinusitis

A. General Characteristics

1. There is inflammation of the lining of the paranasal sinuses, often due to infection. Mucosal edema obstructs the sinus openings (ostia), trapping sinus secretions
2. Most cases of acute sinusitis occur as a complication of the common cold or other URIs. (However, fewer than 1% of URIs lead to acute sinusitis.) May also be caused by nasal obstruction due to polyps, deviated septum, or foreign body
3. Classification
   a. Acute bacterial sinusitis—usually due to *Streptococcus pneumoniae, Haemophilus influenzae,* or anaerobes
   b. Other types—viral, fungal, or allergic
4. The most common sinuses involved are the **maxillary sinuses**

Quick HIT

Sinusitis is usually self-limited, but **can be associated with high morbidity.** It can be life-threatening if the infection spreads to bone or to the CNS.

Quick HIT

If a patient has a cold beyond 8 to 10 days, or if the cold symptoms improve and then worsen after a few days ("double-sickening"), consider acute bacterial sinusitis (may be a secondary bacterial infection after a primary viral illness).

B. Clinical Features

1. Acute sinusitis
   a. Nasal stuffiness, purulent nasal discharge, cough
   b. Sinus pain or pressure (location depends on which sinus is involved)—pain worsens with percussion or bending head down
      - Maxillary sinusitis (most common)—pain over the cheeks that **may mimic pain of dental caries**

- Frontal sinusitis—pain in the lower forehead
- Ethmoid sinusitis—retro-orbital pain, or pain in the upper lateral aspect of the nose

c. Fever in 50% of cases

2. Chronic sinusitis
   a. Nasal congestion, postnasal discharge
   b. Pain and headache are usually mild or absent; fever is uncommon
   c. By definition, symptoms should be present **for at least 2 to 3 months**
   d. In addition to the organisms listed for acute sinusitis, patients with a history of multiple sinus infections (and courses of antibiotics) are at risk for infection with *S. aureus* and gram-negative rods

C. Diagnosis

1. Diagnosis is based on clinical findings. Consider acute bacterial sinusitis if a patient has a cold for more than 8 to 10 days or has prolonged nasal congestion
2. Physical examination
   a. Look for purulent discharge draining from one of the turbinates
   b. Perform transillumination of maxillary sinuses (note impaired light transmission)—the room must be completely dark with a strong light source
   c. Palpate over the sinuses for tenderness (not a reliable finding)
3. Imaging studies—usually not indicated in routine community-acquired infections
   a. Conventional sinus radiographs—look for air–fluid levels in acute disease
   b. A CT scan (coronal view) is superior to a plain radiograph. It should be performed in complicated disease or if surgery is being planned

Quick HIT

Treat with antibiotics and decongestants for 1 to 2 weeks, depending on severity. If there is no improvement after 2 weeks of therapy, then sinus films and a penicillinase-resistant antibiotic are appropriate. Consider ENT consultation. Because of the anatomic difficulties in drainage, the course of acute sinusitis takes longer to resolve than other URIs.

D. Complications

1. Mucocele, polyps
2. Orbital cellulitis—usually originating from ethmoid sinusitis
3. Osteomyelitis of the frontal bones or maxilla
4. Cavernous sinus thrombosis (rare)
5. Very rare—epidural abscess, subdural empyema, meningitis, and brain abscess—due to contiguous spread through bone or via venous channels

Quick HIT

Antihistamines have a drying effect (making secretions thicker) and can sometimes worsen congestion. If this occurs, avoid decongestants with antihistamines.

E. Treatment

1. Acute purulent sinusitis
   a. General measures/advice for the patient
      - Saline nasal spray aids drainage
      - Avoid smoke and other environmental pollutants

   b. Decongestants (pseudoephedrine or oxymetazoline)
      - **Facilitate sinus drainage** and relieve congestion
      - Available in both topical and systemic preparations
      - Given for no more than 3 to 5 days

   c. Antibiotics
      - Amoxicillin, amoxicillin-clavulanate, TMP/SMX, levofloxacin, moxifloxacin, and cefuroxime are good choices

   d. Antihistamines

- Reserve for patients with allergies; use discriminately because of the “drying effect”
- Loratadine (Claritin), fexofenadine (Allegra), chlorpheniramine (Chlor-Trimeton)

e. Nasal steroids (fluticasone, beclomethasone)—may be worth a trial if sinusitis is secondary to allergic rhinitis or if there is concurrent allergic rhinitis

2. Chronic sinusitis
   a. Treat with a broad-spectrum penicillinase-resistant antibiotic
   b. Refer to an otolaryngologist—endoscopic drainage may be necessary

Laryngitis

- Usually viral in origin; may also be caused by *Moraxella catarrhalis* and *H. influenzae*
- Common cause of hoarseness; cough may be present along with other URI symptoms
- Typically self-limiting
- Patient should rest voice until laryngitis resolves to avoid formation of vocal nodules

Quick HIT

Think of the following if a patient has a sore throat:

- Viral infection
- Tonsillitis (usually bacterial)
- **Strep throat**
- Mononucleosis

Quick HIT

Only 50% of patients with pharyngeal exudates have strep throat, and only 50% of patients with strep throat have exudates.

Sore Throat

A. General Characteristics

1. Causes of sore throat
   a. Viruses are by far the most common cause (adenovirus, parainfluenza, rhinovirus, Epstein–Barr virus, herpes simplex)
   b. **The main concern is infection with group A β-hemolytic streptococcus due to the possibility of rheumatic fever**
   c. Other organisms
      - Chlamydia, Mycoplasma
      - Gonococci (oral sex)
      - *Corynebacterium diphtheriae*—pseudomembrane covering pharynx
      - *Candida albicans* (if immunosuppressed, on antibiotics, or severely ill)
2. Viral versus bacterial infection—often difficult to distinguish, but if patient has a cough and runny nose, viral is more likely

B. Diagnosis

1. Throat culture—takes 24 hours, but is more accurate than rapid strep test
2. Rapid strep test—results within 1 hour, but will not indicate whether sore throat is caused by a bacterium other than *Streptococcus* or a virus
   a. Centor criteria: helps predict the likelihood of Strep throat and the appropriate management
      - One point each for history of fever, tonsillar exudates, tender anterior cervical lymphadenopathy, absence of cough, age <15 years; age >44 years subtracts one point
      - –1, 0, or 1 point: No antibiotic, no throat culture
      - 2 or 3 points: Throat culture, treat with antibiotic if throat culture is positive
      - 4 or 5 points: Treat empirically with an antibiotic
3. If mononucleosis is suspected, obtain the appropriate blood tests (Monospot)

C. Treatment

1. If strep throat—penicillin for 10 days (erythromycin if patient has penicillin allergy)
2. If viral—symptomatic treatment (see below)
3. If mononucleosis—advise rest and acetaminophen/ibuprofen for symptoms; avoid contact sports since there is splenomegaly and a risk of splenic rupture
4. Symptomatic treatment of sore throat
   a. Acetaminophen or ibuprofen
   b. Gargling with warm salt water
   c. Use of a humidifier
   d. Sucking on throat lozenges, hard candy, flavored frozen desserts (such as Popsicles)

> ***Quick* HIT**
>
> Most cases (up to 90%) of dyspepsia/heartburn are due to PUD, GERD, gastritis, or nonulcer dyspepsia.

Gastrointestinal Diseases

Dyspepsia

A. General Characteristics

1. "Dyspepsia" refers to a spectrum of epigastric symptoms, including heartburn, "indigestion," bloating, and epigastric pain/discomfort.
2. Dyspepsia is extremely common, and sometimes is confused with angina.
3. Etiology
   a. GI causes—**peptic ulcer disease (PUD), GERD, nonulcer dyspepsia (functional dyspepsia), gastritis,** hepatobiliary disease (cholecystitis, biliary colic), malignancy (gastric, esophageal),

pancreatic disease (pancreatitis, pseudocyst, cancer), esophageal spasm, hiatal hernia.

b. Other causes include lactose intolerance, malabsorption, DM (gastroparesis), and irritable bowel syndrome (IBS).

Quick HIT

Nonulcer Dyspepsia

- A diagnosis of exclusion after appropriate tests (including endoscopy) does not reveal a specific cause.
- Dyspepsia symptoms must be present for at least 4 weeks to make the diagnosis of nonulcer dyspepsia.

B. Diagnosis

1. Base the decision to perform tests on clinical presentation and response to empiric therapy.
2. **Endoscopy** is the test of choice for evaluation of dyspepsia.
   a. It can identify an esophageal stricture or ulcer, cancer, and reflux esophagitis.
   b. It should **not** be routinely performed in all patients with dyspepsia. Some general indications include:
      - Patients with alarming symptoms—weight loss, anemia, dysphagia, or obstructive symptoms.
      - Patients 60 years of age and older with new-onset dyspepsia.
      - Patients with recurrent vomiting or any evidence of upper GI bleeding.
      - Patients who do not respond to empiric therapy (see below).
      - Patients with signs of complications of PUD.
      - Patients with recurrent symptoms.
      - Patients with evidence of systemic illness.
3. Noninvasive testing for *Helicobacter pylori:* an option if the patient does not require an EGD.
   a. Urea breath test: detects active infection.
   b. Serology: cannot reliably determine active infection (antibodies may persist after *H. pylori* is cleared).
   c. Stool antigen test: detects active infection.

d. Results
- If positive, treat for *H. pylori*.
- If negative, PUD is unlikely and the patient likely has either GERD or nonulcer dyspepsia (treat empirically—see below).

C. Treatment

1. Treat the cause if known
2. Advise the patient to:
   a. Avoid alcohol, caffeine, and other foods that irritate the stomach
   b. Stop smoking
   c. Raise the head of the bed when sleeping
   d. Avoid eating before sleeping
3. Use a proton pump inhibitor (PPI) trial for 8 weeks. Endoscopy is indicated if this fails to relieve symptoms
4. Eradication of *H. pylori* infection—see Chapter 3

> ***Quick* HIT**
>
> If GERD is associated with dysphagia, this suggests the development of **peptic stricture.** Alternatively, a motility disorder or cancer may be present.

Gastroesophageal Reflux Disease

A. General Characteristics

1. GERD is a multifactorial problem. Inappropriate relaxation of the LES **(decreased LES tone)** is the primary mechanism, leading to retrograde flow of stomach contents into the esophagus. Other factors that may contribute include:
   a. Decreased esophageal motility to clear refluxed fluid
   b. A gastric outlet obstruction
   c. **A hiatal hernia (common finding in patients with GERD)**
   d. Dietary factors (e.g., alcohol, tobacco, chocolate, high-fat foods, coffee)—may decrease LES pressure and exacerbate the condition
2. GERD is a very common condition. Its prevalence increases with age

Quick HIT

Diagnostic tests are usually not necessary for typical, uncomplicated cases of GERD, and therapy can be initiated. Tests are indicated in atypical, complicated, or persistent cases (despite treatment). Endoscopy should be performed if worrisome symptoms (anemia, weight loss, or dysphagia) are present.

B. Clinical Features

1. Heartburn, dyspepsia
   a. Retrosternal pain/burning shortly after eating (especially after large meals)
   b. Exacerbated by lying down after meals
   c. May mimic cardiac chest pain (which may lead to unnecessary workup for ischemic heart disease)
2. Regurgitation
3. Waterbrash—reflex salivary hypersecretion
4. Cough—due to either aspiration of refluxed material or a reflex triggered by acid reflux into the lower esophagus
5. Hoarseness, sore throat, feeling a lump in the throat
6. Early satiety, postprandial nausea/vomiting

Quick HIT

GERD is a chronic disorder. Regular follow-up is recommended to identify any complications (e.g., Barrett esophagus, stricture, esophagitis).

C. Diagnosis

1. **Endoscopy with biopsy**—the test of choice but not necessary for typical uncomplicated cases.
   a. Indicated if heartburn is refractory to treatment, or is accompanied by dysphagia, odynophagia, or GI bleeding.
   b. A biopsy should also be performed to assess changes in esophageal mucosa.
2. Upper GI series (barium contrast study)—this is only helpful in identifying complications of GERD (strictures/ulcerations), but cannot

diagnose GERD itself.

3. Twenty-four–hour pH monitoring in the lower esophagus—this is the most sensitive and specific test for GERD. It is the gold standard, but is usually unnecessary.
4. Esophageal manometry—use if a motility disorder is suspected.

D. Complications

1. Erosive esophagitis—these patients are at high risk of developing complications such as stricture, ulcer, or Barrett esophagus. These patients are candidates for long-term PPI therapy (see below)
2. Peptic stricture
   a. Consists of fibrotic rings that narrow the lumen and obstruct the passage of food
   b. Presents with dysphagia; may mimic esophageal cancer
   c. EGD can confirm the diagnosis. Dilation should be performed
3. Esophageal ulcer—possible cause of upper GI bleeding
4. Barrett esophagus—occurs in 10% of patients with chronic reflux
   a. The normal stratified squamous epithelium of the distal esophagus is replaced by columnar epithelium. Dysplastic changes may occur, with risk of adenocarcinoma
   b. Patients who have had symptomatic GERD for at least 5 years (and can undergo surgery if cancer is found) should be screened for the possibility of Barrett esophagus
   c. Endoscopy with biopsy is required. If the patient has documented Barrett esophagus without any dysplastic changes, periodic surveillance is appropriate (every 3 years)
   d. Medical treatment—long-term PPIs
5. Recurrent pneumonia (due to recurrent pulmonary aspiration)—the cytologic aspirate finding on bronchoscopy that can diagnose aspiration of gastric contents is **lipid-laden macrophages** (from phagocytosis of fat)
6. Pitting of dental enamel (dental erosion); gingivitis
7. Laryngitis, pharyngitis

E. Treatment

1. Initial treatment:

a. Behavior modification—diet (avoid fatty foods, coffee, alcohol, orange juice, chocolate; avoid large meals before bedtime); sleep with trunk of body elevated; stop smoking
b. Antacids—after meals and at bedtime
2. Add an H_2-blocker—can be used instead of or in addition to antacids for mild and intermittent symptoms
3. If above treatment fails or patient has severe GERD (e.g., erosive esophagitis), switch to a PPI
4. Antireflux surgery for severe or resistant cases
   a. Indications for surgery
      - Intractability (failure of medical treatment)
      - Respiratory problems due to reflux and aspiration of gastric contents
      - Severe esophageal injury (ulcer, hemorrhage, stricture, Barrett esophagus)
   b. Types of surgery
      - Nissen fundoplication (may be done open or laparoscopically)—procedure of choice for a patient with normal esophageal motility
      - Partial fundoplication—when esophageal motility is poor
   c. Outcome of surgery—excellent results have been reported

Diarrhea

A. General Characteristics

1. Most cases of diarrhea are acute, benign, and self-limited (see also Clinical Pearl 12-4). Some cases are chronic and may be associated with underlying disease.
2. Acute diarrhea is diarrhea that lasts less than 2 to 3 weeks; chronic diarrhea lasts more than 4 weeks.
3. Most common cause of acute diarrhea is viral infection (rotavirus and the Norwalk virus are the most common). Most severe forms of acute diarrhea are due to bacterial infections (*Shigella, Escherichia coli, Salmonella, Campylobacter, Clostridium perfringens, Clostridium difficile*). Protozoa that may cause diarrhea include *Giardia lamblia, Entamoeba histolytica,* and *Cryptosporidium.*

4. Elderly and immunocompromised patients (e.g., with HIV, transplantation patients) are vulnerable to diarrheal illnesses due to impaired immunity. In patients with HIV, diarrhea can be caused by *Mycobacterium avium-intracellulare, Cryptosporidium, Cyclospora,* or CMV.

CLINICAL PEARL 12-4

Diarrhea Pearls

- Acute diarrhea is usually due to infection (virus, bacteria, and parasite) or medications.
- If nausea and vomiting are present, suspect viral gastroenteritis or food poisoning.
- If food poisoning is the cause, diarrhea appears within hours of the meal.
- Remember that occult blood in the stool may be present in all types of acute infectious diarrhea, but it is much less common to have gross blood.
- A finding of fever and blood together is typical of infection with Shigella, Campylobacter, Salmonella (may also be without blood), or enterohemorrhagic E. coli.
- No fever and no blood is typical of infection with viruses (rotavirus, Norwalk virus), enterotoxic *E. coli,* and food poisoning (*S. aureus, C. perfringens*).

B. Causes

1. Acute diarrhea
   a. **Infection**—viruses most common (viral gastroenteritis), followed by bacteria, then parasites
   b. **Medications**
      - Antibiotics (most common cause)—antibiotic-associated diarrhea is caused by *C. difficile* toxin in 25% of cases (see Chapter 3)
      - Others include laxatives, prokinetic agents (cisapride), antacids, digitalis, colchicine, alcohol, magnesium-containing antacids, and chemotherapeutic agents
   c. Malabsorption (e.g., lactose intolerance)
   d. Ischemic bowel in elderly patients with history of PAD and bloody diarrhea, along with abdominal pain
   e. Intestinal tumors (very rare)
2. Chronic diarrhea (see Figure 12-4)

Quick HIT

Assess volume status (dehydration is a concern), perform an abdominal examination, and check stool for occult blood in patients with diarrhea. In mild-to-moderate cases of acute diarrhea, further workup is unnecessary.

Quick HIT

Laboratory tests to consider:

- Stool WBCs
- Stool for ova and parasites (O&P)
- Stool culture
- Stool for *C. difficile* toxin assay
- Stool for *Giardia* antigen

C. Diagnosis

1. Laboratory tests are usually unnecessary in acute diarrhea (see Clinical Pearl 12-5)
2. Some indications for diagnostic studies
   a. Chronic diarrhea or diarrhea that is prolonged
   b. Severe illness or high fever
   c. Presence of blood in the stool/high suspicion for IBD
   d. Severe abdominal pain
   e. Immunodeficiency
   f. Signs of volume depletion
3. Laboratory tests to consider
   a. CBC—look for anemia, WBC elevation
   b. Testing for *C. difficile* with a toxin assay
   c. Stool sample—for presence of fecal leukocytes
      - If fecal leukocytes are absent, there is no need to order stool cultures because they are unlikely to grow pathogenic organisms (unless invasive bacterial enteritis is suspected or the patient has bloody diarrhea)

   d. Stool sample—test three samples for presence of ova and parasites. Order this if a parasite is suspected. For *Giardia*, order enzyme-linked immunosorbent assay (ELISA) test for antigen

e. Bacterial stool culture
   - This has low sensitivity (and is an expensive test), and usually does not affect treatment or outcome
   - It should not be ordered routinely. Some indications include: if invasive bacterial enteritis is suspected, if the patient has moderate-to-severe illness or fever, if the patient requires hospitalization, and if the stool sample is positive for fecal leukocytes
   - Most laboratory tests examine stool culture for only three organisms: *Shigella, Salmonella,* and *Campylobacter*

f. Colonoscopy/flexible sigmoidoscopy—may be considered for patients with blood in the stool or for patients with chronic diarrhea for which a cause cannot be identified

g. CT scan may be helpful if IBD or diverticulitis is suspected; colonoscopy should not be performed during a flare due to the risk of bowel perforation

CLINICAL PEARL 12-5

Important Parts of the History in a Patient With Diarrhea

- Is the stool bloody or melanotic?
- Are there any other symptoms (e.g., fever, abdominal pain, vomiting)?
- Is there anyone in the family or group with a similar illness?
- Has there been any recent travel outside the United States, or any hiking trips (parasitic infections)?
- Are symptoms linked to ingestion of certain foods (e.g., milk)?
- Are there any medical problems (e.g., AIDS, hyperthyroidism)?
- Have there been recent changes in medications (e.g., antibiotics within the past few weeks)?

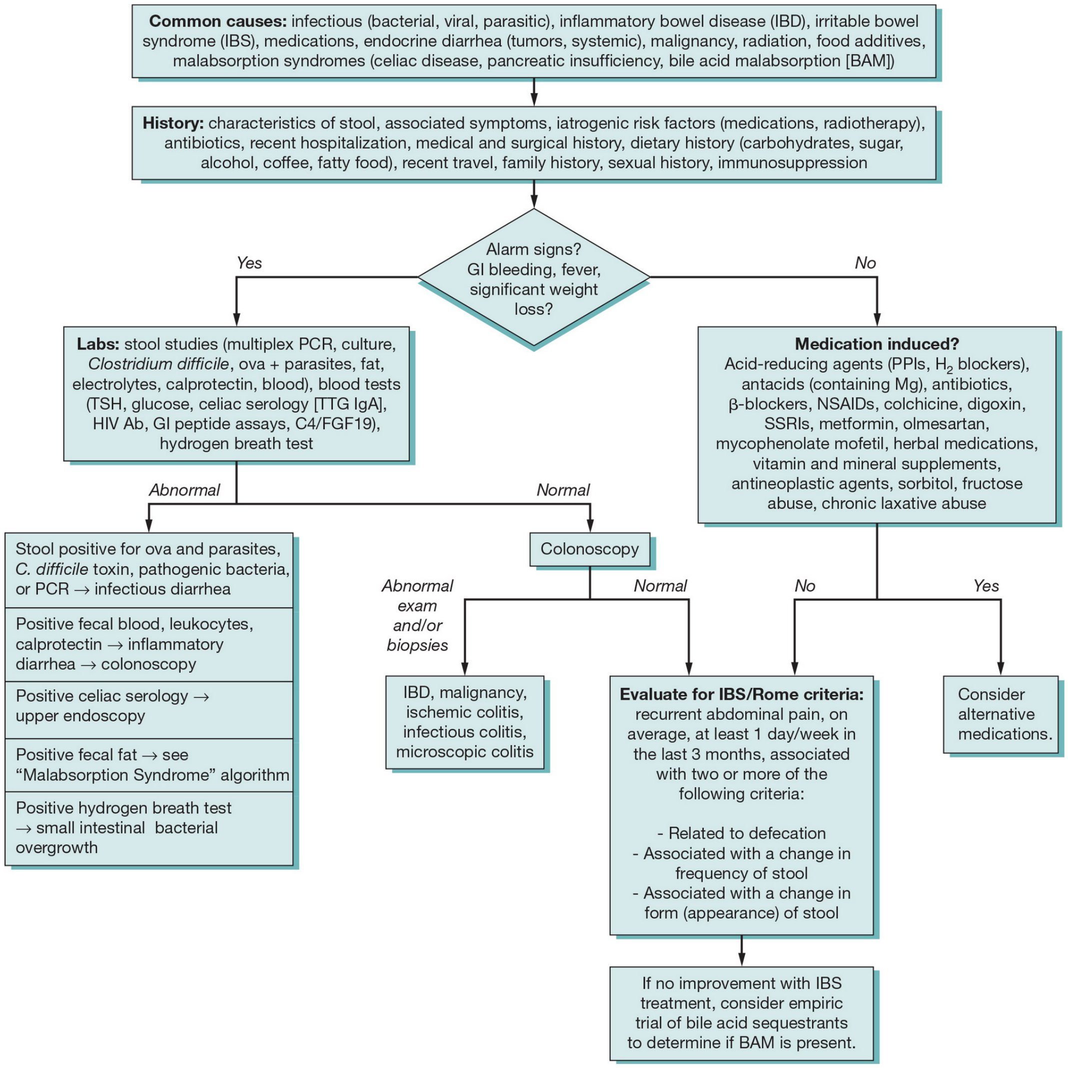


FIGURE 12-4 Chronic diarrhea.

(Reprinted with permission from Domino FJ, Baldor RA, Barry KA, et al. *The 5-Minute Clinical Consult 2023*. 31st ed. Wolters Kluwer; 2022. [Data from Schiller LR. Evaluation of chronic diarrhea and irritable bowel syndrome with diarrhea in adults in the era of precision medicine. *Am J Gastroenterol*. 2018;113(5):660–669.])

Quick HIT

Salmonella, Campylobacter, Shigella, and enteroinvasive *E. coli* cause diarrhea with fecal leukocytes and often blood.

Quick HIT

The most common electrolyte/acid–base abnormalities seen with severe diarrhea are **metabolic acidosis** and **hypokalemia.**

D. Treatment

1. Acute diarrhea is typically self-limited and does not require hospitalization. However, consider hospitalization for any of the following reasons:
   a. Dehydration (especially in elderly patients)
   b. Patients initially unable to tolerate or hold down PO fluids
   c. Bloody diarrhea (with profuse or brisk bleeding)
   d. High fever, toxic appearance
2. The identification of the specific agent responsible for acute infectious diarrhea is not critical with regard to treatment. Treat the diarrhea according to the patient's medical history and clinical condition
3. Specific therapy
   a. Rehydrate; monitor electrolytes and replace if necessary
   b. Treat the underlying cause (e.g., stop or change medication, advise a lactose-free diet). Consider a trial of NPO status to see if diarrhea stops
   c. Consider antibiotics. Use of antibiotics in **infectious** diarrhea has been shown to decrease the duration of illness by 24 hours (regardless of the etiologic agent). Therefore, consider a 5-day course of ciprofloxacin in patients who have moderate-to-severe disease. Antibiotics are definitely recommended in the following situations:
      - Patient has high fever, bloody stools, or severe diarrhea—quinolones are appropriate
      - Stool culture grows one of the pathogenic organisms (see Table 12-4)
      - Patient has traveler's diarrhea
      - *C. difficile* infection
4. Loperamide (Imodium) is an antidiarrheal agent that should only be given if diarrhea is mild to moderate and is not recommended in patients with fever or with blood in their stool

Constipation

A. Causes

1. Diet—lack of fiber
2. Medications—anticholinergic drugs (antipsychotics), antidepressants, **narcotic analgesics,** iron, calcium channel blockers, aluminum- or calcium-containing antacids, laxative abuse, and dependence
3. IBS
4. Obstruction—colorectal cancer (CRC) (always keep this in mind!), anal stricture, hemorrhoids, anal fissure
5. Ileus, pseudo-obstruction
6. Anorectal problems—hemorrhoids, fissures
7. Endocrine/metabolic causes—hypothyroidism, hypercalcemia, hypokalemia, uremia, dehydration
8. Neuromuscular disorders—Parkinson disease, multiple sclerosis, CNS lesions, scleroderma, DM (autonomic neuropathy)
9. Congenital disorders—Hirschsprung disease

Quick HIT

Complications of Chronic Constipation

- Hemorrhoids
- Rectal prolapse
- Anal fissures
- Fecal impaction

B. Diagnosis

1. Laboratory tests that **may** be necessary include TSH, serum calcium levels, CBC (if colon cancer is suspected), and electrolytes (if obstruction is suspected).
2. Always attempt to rule out obstruction.
   a. If H&P is suggestive of obstruction, order abdominal films.
   b. Consider flexible sigmoidoscopy in selected cases (if an obstructing colorectal mass is suspected).

3. A rectal examination may help identify fissures, hemorrhoids, fecal impaction, or masses.
4. If no cause is found after the above measures, and conservative treatment does not help, more specialized tests are available—for example, radiopaque marker transit study, anorectal motility study.

TABLE 12-4 Common Pathogens Responsible for Acute Infectious Diarrhea

Pathogen	Symptoms	Fever?	Fecal Leukocytes	Duration of Illness	Transmission	Comments
Acute viral gastroenteritis (rotavirus, Norwalk virus)	**Myalgias, malaise,** headache, watery diarrhea, abdominal pain, **nausea/vomiting**	Possible, low grade	No	48–72 hrs, symptoms may linger for up to 1 wk	Fecal–oral route	Most common cause of acute diarrhea in the United States Look for similar illness in family members
Salmonella	Abdominal pain, diarrhea, nausea, and vomiting	Possible	Yes	Resolves within 1 wk (rarely longer)	Food (domestic fowl and their eggs—most common); fecal–oral route as well	Symptoms appear 24–48 hrs after ingesting food. No treatment is required except in immunocompromised patients or in cases of enteric fever (caused by *Salmonella typhi*)—rare in the United States. Ciprofloxacin (Cipro) is the preferred agent
Shigella	Diarrhea, abdominal pain, **tenesmus;** nausea, vomiting less common	Possible	Yes	Resolves within 1 wk (4–5 days)	Fecal–oral route more common than food	Treat with a fluoroquinolone
Staphylococcus food poisoning	Abdominal pain, nausea and vomiting, diarrhea	No	No	**Within 24 hrs**	Food (e.g., ham, poultry, potato salad, any food containing mayonnaise)	Exposed people become ill **within 1–6 hrs** (e.g., after a picnic). Can be quite severe and may require hospitalization
Campylobacter jejuni	Headache, fatigue followed by diarrhea and abdominal pain	Yes	Yes	Less than 1 wk	Food (e.g., contaminated meat, especially poultry), animals (e.g., puppies, kittens)	Most common cause of acute bacterial diarrhea. Can be severe: blood appears in stool in 50% of cases. Treat with fluoroquinolone or azithromycin. Relapses may occur
C. perfringens	Diarrhea; **crampy abdominal pain is prominent;** vomiting and fever are rare	No	No	Within 24 hrs	Food (poultry, gravy)	Illness begins soon after ingesting food (within 12–24 hrs)
Enterotoxic *E. coli* ("travelers' diarrhea")	Watery diarrhea, nausea, abdominal pain	No	No	Few days	Contaminated food and water	Self-limiting disease is common in developing countries.
E. coli 0157:H7	Bloody diarrhea; patient can appear very sick	Yes	Yes		Food (undercooked meat, raw milk)	Hemorrhagic colitis that is usually self-limited, but has been associated with hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP); supportive treatment, do not give antibiotics (induces the release of Shiga toxin, increasing the risk of HUS/TTP)
Giardiasis	Watery, foul-smelling diarrhea; abdominal bloating	No	No	5–7 days, sometimes longer	Fecal–oral route, food, or contaminated water	Treat with metronidazole; can become chronic
Vibrio cholerae	Voluminous diarrhea ("rice water" stools), abdominal pain, vomiting	Low grade	No			Rare in the United States, but common in developing countries

C. Treatment

1. Diet and behavioral modification are the most important aspects of treatment. Advise the patient to:
   a. Increase physical activity
   b. Eat high-fiber foods
   c. Increase fluid intake
2. Bulk laxatives are preferred over osmotic laxatives in patients that do not respond to diet and lifestyle changes
3. Use an enema, such as a disposable Fleet enema, for temporary relief if no bowel movement occurs despite the above measures or if the patient is bedridden
4. If obstruction is present, urgent surgery consultation is indicated

Irritable Bowel Syndrome

A. General Characteristics

1. IBS refers to an idiopathic disorder associated with an intrinsic bowel motility dysfunction (abnormal resting activity of GI tract) that affects 10% to 15% of all adults.
2. Common associated findings include depression, anxiety, and somatization. Psychiatric symptoms often precede bowel symptoms. **Symptoms are exacerbated by stress and irritants in the intestinal lumen.**
3. All laboratory test results are normal, and no mucosal lesions are found on sigmoidoscopy. IBS is a benign condition and has a favorable long-term prognosis.
4. Symptoms should be present for **at least 3 months** to diagnose IBS.

B. Clinical Features

1. Change in frequency/consistency of stool—diarrhea, constipation (or alternating diarrhea and constipation)
2. Cramping abdominal pain (relieved by defecation)—location varies widely, but sigmoid colon is the common location of pain
3. Bloating or feeling of abdominal distention

Quick HIT

Differential Diagnosis of IBS

Colon cancer, IBD, drugs, mesenteric ischemia, celiac disease, ischemic colitis, giardiasis, pseudo-obstruction, depression, intermittent sigmoid volvulus, megacolon, bacterial overgrowth syndrome, endometriosis.

C. Diagnosis

1. This is a clinical diagnosis, and a diagnosis of exclusion.
2. Rome IV diagnostic criteria: recurrent abdominal pain/discomfort ≥1 day per week in the last 3 months, and ≥2 of the following:
   a. Pain/discomfort changes with defecation.
   b. Symptom onset is associated with a change in the frequency of the stool.
   c. Symptom onset is associated with a change in the form of the stool.
3. Initial tests that may help exclude other causes include CBC, fecal calprotectin, stool examination for infections including giardia, celiac disease testing. If any red flags or unusual features, endoscopy should be considered.

D. Treatment

1. For mild symptoms, diet and lifestyle changes (e.g., avoiding dairy products, excess caffeine). Manage the symptoms below as indicated:
   a. Diarrhea—diphenoxylate, loperamide, bile acid sequestrants, rifaximin.
   b. Constipation—polyethylene glycol, psyllium, lubiprostone, linaclotide.
   c. Abdominal pain—antispasmodics (e.g., pinaverium, trimebutine, peppermint oil, cimetropium/dicyclomine), antidepressants.

Quick HIT

Gastroenteritis

- Typically caused by an enterovirus, and is seen in groups among family members, colleagues, and so on.
- Diarrhea is often present as well, but may appear later.

Nausea and Vomiting

A. General Characteristics

1. The most common causes are viral gastroenteritis and food poisoning. However, other more emergent diseases must be kept in mind.
2. Many conditions present with other prominent symptoms (e.g., abdominal pain, diarrhea, fever) in addition to nausea/vomiting.

CLINICAL PEARL 12-6

Causes of Acute Nausea/Vomiting

- Pregnancy (normal pregnancy, hyperemesis gravidarum)
- Metabolic: diabetic ketoacidosis, Addison disease, uremia, electrolyte disturbance (hypercalcemia, hypokalemia), hyperthyroidism
- GI: gastroenteritis (viral, food poisoning), PUD, GERD, gastroparesis (diabetics), gastric outlet obstruction, intestinal obstruction (SBO, pseudo-obstruction), ileus, peritonitis
- Acute visceral conditions: pancreatitis, appendicitis, pyelonephritis, cholecystitis, cholangitis
- Neurologic: increased intracranial pressure, vestibular disturbance (vertigo), migraine
- Acute MI
- Drugs: chemo, digoxin, ASA/NSAIDs, opioids, antibiotics, excessive alcohol intake
- Psychiatric: eating disorder (bulimia nervosa, anorexia nervosa), anxiety
- Miscellaneous: motion sickness, systemic illness, radiation therapy, postoperatively

B. Approach

1. Questions to ask when taking the history: Recent food intake (Unusual foods? Time of onset of vomiting in relation to food intake? Did anyone else eat that food?) (Clinical Pearl 12-6). Are symptoms related to meals? Ask about medications and recent changes/additions. Is there a history of abdominal surgery (obstruction) or recent surgery? Are there family members with a similar illness?
2. Define the vomitus
   a. Bilious—obstruction is distal to ampulla of Vater
   b. Feculent—distal intestinal obstruction, bacterial overgrowth, gastrocolic fistula
   c. Vomiting of undigested food—esophageal problem more likely (achalasia, stricture, diverticulum)
   d. Projectile vomiting—increased intracranial pressure or pyloric stenosis
   e. Coffee-ground material or blood—GI bleeding
3. Accompanying symptoms
   a. Diarrhea and fever point to an infectious process (gastroenteritis)
   b. Abdominal pain points to obstruction, acute inflammatory conditions (e.g., peritonitis, cholecystitis)
   c. Headache, visual disturbances, and other neurologic findings point to increased intracranial or intraocular pressure (IOP)

Quick HIT

Possible Complications of Severe or Prolonged Vomiting

- Fluid/electrolytes—dehydration, metabolic alkalosis, hypokalemia
- Dental caries
- Aspiration pneumonitis
- GI: Mallory–Weiss tears, Boerhaave syndrome, Mallory–Weiss syndrome

C. Diagnosis

1. Order routine laboratory tests such as CBC, electrolytes, glucose levels, LFTs, if appropriate, based on history and examination findings.
2. Order a pregnancy test in women of child-bearing age.

3. Abdominal films—order upright and supine films in patients with acute vomiting if obstruction or perforation is suspected.
4. Order other diagnostic tests depending on clinical findings (e.g., upper GI endoscopy for ulcer disease or outlet obstruction, ultrasound for biliary disease, CT scan of head for neurologic findings).
5. In at least 50% of patients, the above tests do not reveal a cause. Special tests for GI motility may be indicated if there is suspicion of a motility disorder.

Quick HIT

The most common electrolyte abnormality seen after severe vomiting is **hypokalemia with metabolic alkalosis.**

D. Treatment

1. Most causes are self-limiting. If vomiting is severe, it may cause dehydration, requiring hospitalization.
2. Assess hydration status—fluid replacement is the first step in management, NS is used in most cases (but type of fluid and electrolyte repletion based on laboratory findings).
3. Identify and treat the underlying cause if possible.
4. Medications—choice of drug depends on the suspected cause (e.g., promethazine for hyperemesis gravidarum). Common first-line options include antiemetics and prokinetics: ondansetron, metoclopramide, prochlorperazine, erythromycin. Benzodiazepines (e.g., lorazepam) can be tried in cases of prolonged QTc and is good for anticipatory nausea. There are many other options for second-line agents, and many are included in chemotherapy regimens.

Hemorrhoids

A. General Characteristics

1. Varicose veins of anus and rectum
2. Two types

a. External hemorrhoids (painful)—dilated veins arising from inferior hemorrhoidal plexus; distal to dentate line (sensate area)
b. Internal hemorrhoids (not painful)—dilated submucosal veins of superior rectal plexus; above dentate line (insensate area)

B. Risk Factors

1. Constipation/straining
2. Pregnancy
3. Portal HTN
4. Obesity
5. Prolonged sitting (especially truck drivers and pilots) or prolonged standing
6. Anal intercourse

C. Clinical Features

1. Bleeding and rectal prolapse (main symptoms)
   a. Bright red blood per rectum
   b. Bleeding from hemorrhoids is usually harmless, but occult rectal bleeding should prompt an investigation into more serious causes and should never be attributed to hemorrhoids until other conditions are ruled out
   c. Bleeding is usually painless
2. External hemorrhoids are usually asymptomatic unless thrombosed, in which case they present as sudden painful swelling (may ulcerate, bleed). Pain lasts for several days, and then gradually subsides. The response to surgery is rapid
3. Internal hemorrhoids usually do not cause pain. A mass is present when they prolapse

D. Treatment

1. General measures to ease symptoms
   a. Sitz bath
   b. Application of ice packs to anal area and bed rest
   c. Stool softeners to reduce strain
   d. High-fiber, high-fluid diet
   e. Topical steroids

2. Rubber band ligation for internal hemorrhoids—rubber bands applied to hemorrhoidal bundle(s) leads to necrosis and sloughing of lesion
3. Surgical (hemorrhoidectomy)—perform surgery if the condition does not respond to conservative methods, or if severe prolapse, strangulation, very large anal tags, or fissure is present. Surgery can be performed in an outpatient setting

Quick HIT

Most Common Causes of LBP

- Musculoligamentous strain
- Degenerative disc disease
- Facet arthritis

MUSCULOSKELETAL PROBLEMS

Overview of Musculoskeletal Examination Maneuvers

Low Back Pain

A. General Characteristics

1. Second most common reason for medical office visits in the United States (Table 12-5).
2. Acute low back pain (LBP) refers to symptoms present for less than 4 weeks, subacute is 4 to 12 weeks, and chronic LBP refers to pain lasting more than 12 weeks. The natural history of acute and subacute LBP is very favorable. Management of chronic back pain is very challenging.
3. Risk factors for chronic LBP: smoking, obesity, older age, sedentary work, physically strenuous work, psychologically strenuous work, low

educational attainment, worker's compensation insurance, job dissatisfaction, psychological factors (depression, anxiety, etc.)

4. Majority of patients present with "nonspecific" or mechanical back pain, meaning there is no significant underlying cause such as neoplasm or infection or spine pathology.
5. If patient has significant radicular leg pain, nerve compression is likely. If leg symptoms are severe, or if objective weakness is present, an MRI of lumbar spine is obtained. An MRI is unnecessary in most patients who present with an acute episode of pain.

TABLE 12-5 Important Musculoskeletal Physical Examination Maneuvers

General	
Important aspects include observation (asymmetry, atrophy, etc.), palpation of important landmarks (joint line, surrounding muscles, and tendons, etc.), active and passive range of motion, assessment of muscle strength, and special testing (below) when a diagnosis is suspected.	
Neck	
Spurling maneuver	• Technique: patient asked to extend neck, rotate and tilt to side of pain while downward pressure is applied onto head • High specificity but low sensitivity for **cervical root compression**, which is suggested by reproduction of the pain below the shoulder joint (radicular pain)
Shoulder	
Empty can test	• Technique: arms held out in front of the patient parallel to the ground with thumbs pointed downward. Resistance is applied by the examiner and the patient tries to maintain the position. • Pain with resistance may indicate a **supraspinatus** defect.
External rotation	• Technique: arm is held at patient's side with elbow flexed at 90 degrees. Patient is asked to externally rotate the forearm against resistance. • Pain with resistance may indicate an **infraspinatus** defect.
Lift-off test	• Technique: patient's hand is placed behind their back with the dorsum of the hand against the back. They are asked to lift their hand off their back. • An inability to bring their hand off their back indicates a defect in internal rotation, which may indicate a **subscapularis** defect.
Neer test	• Technique: the patient's arm is fully pronated (thumb pointed downward) and forcibly flexed above their head. • Pain with this maneuver may indicate **rotator cuff impingement**.
Hawkins test	• Technique: patient's arm is abducted to 90 degrees with the elbow bent (as if holding the arm out to catch a *hawk*), and the examiner internally rotates the shoulder. • Pain with this maneuver may indicate **rotator cuff impingement**.
Cross-arm test	• Technique: patient's arm is held in front of them to 90 degrees and the patient actively adducts the arm (crosses it in front of them). • Pain at the acromioclavicular (AC) joint indicates **AC joint dysfunction** (which can be confused with rotator cuff pathology).
Knee	

Varus/valgus stress test	• Technique: examiner stabilizes the knee joint with one hand and uses the other hand to grab the lower leg and apply a lateral force. A varus stress is when the force on the knee is applied toward the body (in a lateral to medial), and a valgus stress is the opposite. • Laxity with a varus stress implies a defect in the **lateral collateral ligament** (LCL), and laxity with a valgus stress implies a defect in the **medial collateral ligament** (MCL).
Lachman and anterior drawer	• Technique: the Lachman test is performed with the knee flexed at 30 degrees whereas the anterior drawer is performed with the knee flexed at 90 degrees. In both examinations, the proximal tibia is pulled anteriorly, away from the femur. • Excessive anterior translation of the tibia suggests an **anterior cruciate ligament** (ACL) tear.
Posterior drawer	• Technique: the patient is placed supine and the knee flexed at 90 degrees. The proximal tibia is pushed posteriorly toward the femur. • Excessive posterior translation of the tibia suggests a **posterior cruciate ligament** (PCL) tear.
McMurray test	• Technique: the knee is passively flexed by the examiner, then externally rotated with a varus stress as the knee is extended. This is repeated with internal rotation. • A painful click or joint line tenderness suggests a **meniscal** injury.

***Quick* HIT**

Factors that Exacerbate Pain in Disc Herniation

- Maneuvers that increase intraspinal pressure, such as coughing or sneezing
- Forward flexion—sitting, driving, or lifting; worsens leg pain

***Quick* HIT**

Majority of patients with lumbar disc herniation and sciatica improve with conservative care. Only about 10% will require surgical intervention.

***Quick* HIT**

Patients with spinal stenosis have leg pain with back extension—pain worsens with standing or walking (relief with bending or sitting).

Quick HIT

Pathology in other organ systems can cause back pain and should be ruled out:

- Vascular disease (aortic aneurysm, aortic dissection)
- Pancreatic disease
- Urologic disease (prostate infection, renal calculi)
- Gynecologic/obstetric disease (endometriosis, ectopic pregnancy, pelvic inflammatory disease)

Quick HIT

Chronic LBP: Imaging findings on MRI do not necessarily correlate with presence or severity of pain. Psychosocial variables are much stronger predictors of pain and disability.

B. Causes

1. There are many causes of LBP. Most patients who present with back pain do not have a specific spine pathology, which is referred to as "nonspecific" LBP.
2. The following conditions can all cause LBP. Note that many patients with these imaging findings do not have back pain. Therefore, imaging findings do not necessarily correlate with symptoms. For example, many patients with degenerative disc disease or spondylolisthesis have no back pain.
   a. Degenerative disc disease (osteoarthritis)—many people with severe degenerative disc disease do not have back pain. Surgery is controversial for this indication.
   b. Spondylolisthesis—forward slippage of cephalad vertebra on the caudal vertebra. Most common at L4–L5 and L5–S1. Spinal stenosis often coexists, leading to neurogenic claudication.
   c. Lumbar disc herniation—radicular leg pain (commonly referred to as sciatica) is the predominant finding, although some patients have back pain as well. Back pain without any radicular pain is uncommon but can occur. Most common at L4–L5 and L5–S1. Treatment is anti-inflammatory medication, physical therapy, and

epidural steroid injections. Surgery indicated when conservative treatment fails or if patient has progressive neurologic deficits.

d. Spinal stenosis—narrowing of spinal canal due to degenerative changes which causes neurogenic claudication. Back pain may coexist, but predominant finding is neurogenic claudication.
   - Neurogenic claudication refers to radicular leg or buttock pain that is caused by spinal stenosis. It can manifest as pain, cramping, numbness, or paresthesias, particularly worse with walking and relieved with sitting. Forward flexion of spine improves symptoms (patients lean on shopping cart).
   - Treat with epidural steroid injections if it is affecting patient's quality of life. Surgery is very effective if conservative treatment fails.

e. Musculoligamentous strain—usually after an episode of bending/twisting, patient feels the back "give way," often when lifting a heavy object, with immediate onset of back pain. Radiation of pain may occur to buttock/upper posterior thigh to knee level—this is called "referred pain" from muscle spasm. Pain typically does not radiate distal to the knee because no nerve root compression is present.

f. Vertebral compression fracture—acute back pain caused by minor stress in elderly or in patients on long-term steroid treatment. Pain is at the level of the fracture with local radiation across the back and around the trunk (rarely to legs).
   - Can occur with minimal or no trauma in patients with osteoporosis.
   - Multiple compression fractures can lead to severe kyphosis in the thoracic spine.
   - Treatment options include bracing (if patient's body habitus allows), analgesics, and giving the fracture time to heal. Most fractures heal in 6 to 8 weeks and symptoms gradually improve. Interventional options include kyphoplasty/vertebroplasty (injection of cement into vertebral body). Recent randomized controlled trials have brought the efficacy of these interventions into question.

g. Neoplasms—most common spinal tumor by far is metastatic carcinoma—common primary neoplasms that metastasize to spine

include breast, lung, prostate, kidney, and thyroid.

h. Infection—discitis or osteomyelitis.
   - Suspect in patients with history of IV drug use, dialysis, indwelling catheter; most common organism is *S. aureus.*
   - Laboratory tests to order include CBC with differential, ESR, and CRP.
   - If suspicion is high, MRI should be obtained.
   - Epidural abscess in the cervical and thoracic spine can lead to rapid neurologic deterioration and in most cases, requires surgical decompression; epidural abscess in the lumbar spine can often be medically managed with antibiotics if there are no neurologic deficits and patient is not septic.

***Quick* HIT**

Major Segmental Innervation of the Lower Limb

- Hip flexion—L2
- Knee extension—L3
- Ankle dorsiflexion—L4 and L5
- Great toe dorsiflexion—L5
- Ankle plantar flexion—S1

C. Back Examination

1. The main goal of the history and physical examination is to rule out any structural or systemic conditions that can be the source of back pain. The neurologic examination is very important, and any weakness should be documented.
2. The straight-leg raise can suggest nerve root compression. The test is positive if radiculopathy is reproduced when the leg is elevated 30 to 60 degrees with the patient supine. If patient is in severe pain and cannot tolerate even a slight elevation of the leg during this test, it is highly suggestive of nerve root compression.

Quick HIT

In general, radiologic imaging is unnecessary in evaluation of LBP. Imaging is appropriate if symptoms do not resolve within 1 month or if there are neurologic signs/symptoms.

D. Diagnostic Tests

1. Imaging is not necessary during the first 4 to 6 weeks in the absence of any of the following—progressive neurologic deficits or disabling symptoms, osteoporosis or prolonged steroid use, constitutional symptoms (unexplained fever or weight loss), history of malignancy, recent trauma, IV drug use (see also Clinical Pearl 12-7).
2. MRI is indicated if patient has failed a course of conservative treatment (rest, physical therapy, NSAIDs) for at least 3 months. Patients with neurologic signs or symptoms should have an MRI sooner, depending on the severity and acuteness of clinical findings.

Quick HIT

It is helpful to differentiate patients with predominantly LBP from those with predominantly leg pain. When conservative treatment has failed, surgery is often effective for leg pain, but results for LBP are less predictable.

E. Treatment

1. Most patients with acute LBP have improvement or resolution within 3 to 6 weeks and are managed with NSAIDs, acetaminophen, activity modification, and gradual return to activities. Narcotic analgesics and muscle relaxants should be used judiciously, if at all. Patients should be advised to continue ordinary activities within the limits permitted by pain. If symptoms do not improve in 4 to 6 weeks, a course of physical therapy for core-strengthening exercises may be helpful.
2. If neurologic deficits present, particularly if these deficits are progressive, a more aggressive approach is indicated. An MRI should be obtained, and if nerve root or spinal cord compression is present, evaluation by a spine specialist is recommended.

3. The treatment of chronic nonspecific LBP is challenging. Most patients with **chronic** LBP with or without radiculopathy are treated conservatively (with physical therapy, NSAIDs, injections).
   a. Physical therapy is focused on core-strengthening exercises and aerobic conditioning.
   b. There is some evidence that massage therapy, chiropractics, and acupuncture may be helpful in the short term, but studies have not been able to show long-term benefits.
   c. If conservative measures fail and symptoms persist for at least 1 year, surgery can be considered, depending on findings on imaging studies and degree of disability. In general, outcomes from surgery are more predictable and successful when surgery is done for radiculopathy (to decompress nerve roots) than for LBP per se. Surgery (fusion) for degenerative disc disease and chronic LBP is controversial, and randomized controlled trials have NOT shown significant benefits. A very small percentage of patients may benefit from surgery but careful patient selection is critical and informed consent about expected outcomes is recommended.

CLINICAL PEARL 12-7

Cauda Equina Syndrome

- Caused by severe stenosis in the lumbar spine, most commonly due to an acute disc herniation.
- Patients present with severe back or leg pain (uni- or bilateral), with or without weakness in the legs. The key findings are bladder dysfunction (retention, incontinence) and saddle anesthesia (numbness in perineal or buttock region).
- Symptoms can have acute onset, or start with leg pain initially and over the ensuing days, progress to weakness and bladder dysfunction.
- This is a surgical emergency. An MRI should be obtained immediately.

Quick HIT

Management of LBP

Avoid prolonged inactivity (leads to deconditioning). In the first week, attempt a walking routine (20 minutes, three times per day, interspersed with bed rest).

Common Disorders of the Cervical Spine

A. General Characteristics

1. Spondylosis (osteoarthritis) of the cervical spine is very common and is not necessarily a source of neck pain. Patients with spondylosis of the cervical spine present with axial neck pain, cervical radiculopathy, or cervical myelopathy.
2. Chronic axial neck pain (without radiating arm pain) is common and just like chronic LBP can be difficult to treat. Many of the principles discussed above for nonspecific LBP apply to nonspecific neck pain as well. Surgery is not a good option for patients with neck pain without radicular arm symptoms.
3. The most common cause of acute neck pain is cervical strain which is usually self-limiting and resolves with time. Physical therapy can be helpful if symptoms last longer than 2 to 4 weeks.

B. Cervical Radiculopathy

1. Compression of a spinal nerve leads to arm pain, numbness, tingling, or weakness. Most common complaint is unilateral neck pain radiating to the arm in a dermatomal pattern.
2. The most common cause is cervical spondylosis (osteoarthritis) and disc herniation. Differential diagnosis includes shoulder pathology (impingement syndrome, rotator cuff disease), peripheral nerve entrapment (carpal tunnel or cubital tunnel syndrome), thoracic outlet syndrome, zoster, and Pancoast tumor (can present with brachial plexus symptoms).
3. The best test to diagnose nerve root compression is MRI of cervical spine.

4. Most patients can be treated conservatively (NSAIDs, time, physical therapy, epidural injections). Surgery is helpful in patients who do not respond to conservative management or who have significant weakness in one or more muscle groups.
5. It is very unusual for a patient with cervical radiculopathy to progress to myelopathy. It appears that these are two distinct entities.

Quick HIT

Shoulder impingement syndrome is often confused with cervical radiculopathy involving the C5 nerve root. If in doubt, inject the shoulder (subacromial space) with cortisone to see if symptoms resolve.

C. Cervical Myelopathy

1. Neurologic dysfunction secondary to spinal cord compression (cervical stenosis) in the cervical spine. Diagnosis made by MRI of cervical spine.
2. Earliest symptom is gait disturbance. Patients feel unsteady when ambulating. Other symptoms include loss of hand dexterity (clumsiness, difficult with buttoning shirts, changes in handwriting), with bowel and bladder dysfunction being late findings.
   a. Pain is not a common finding so patients may go undiagnosed until the myelopathy is severe.
3. Patients often start relying on a cane or walker (due to unsteady gait), and if untreated may eventually lose the ability to walk. Frank weakness is a late finding. In its most advanced stage, patients become nonambulatory, with loss of functional use of upper extremities, and bowel and bladder function.
4. Natural history is gradual deterioration. Treatment is surgery to decompress the spinal cord when diagnosis is made. Conservative treatment does not play a role in the treatment of cervical stenosis with myelopathy. Main goal of surgery is to prevent further neurologic worsening which is why it is important to make the diagnosis early. Once the patient loses the ability to ambulate, it is unlikely to return even with surgery.

Knee Pain

A. Causes

1. Osteoarthritis—most common cause of knee pain in older patients (see below) (see Clinical Pearl 12-8).

CLINICAL PEARL 12-8

Causes of Arthritis

- Osteoarthritis (most common cause)
- Systemic immune disease—rheumatoid arthritis, SLE, seronegative spondyloarthropathies (e.g., reactive arthritis, ankylosing spondylitis, IBD)
- Crystal disease—gout, pseudogout
- Infectious—septic arthritis, Lyme disease
- Trauma
- Charcot joint (diabetes)
- Pediatric orthopedic conditions such as congenital hip dysplasia, Legg–Calvé–Perthes disease, slipped capital femoral epiphysis (SCFE)
- Hematologic—sickle cell disease (avascular necrosis of femoral head), hemophilia (recurrent hemarthrosis)
- Deposition diseases—Wilson disease, hemochromatosis

2. Patellofemoral pain—very common cause of anterior knee pain; worse with climbing and descending stairs. Physical therapy aimed at quadriceps/hamstrings rehabilitation (stretching/strengthening) is very effective.
3. Degeneration or tear of a meniscus—meniscal tears may be due to a specific injury or secondary to a degenerative process (the latter being a common cause of knee pain in older patients). Key features include recurrent knee effusions, tenderness along medial or lateral joint lines, and a positive McMurray test. If no arthritic changes are present, surgery (arthroscopic meniscectomy or repair) is effective. Surgery is less effective when concomitant arthritic changes are present and results are less predictable.

Quick HIT

Patellofemoral pain is a very common cause of anterior knee pain. Send these patients to physical therapy to strengthen/stretch quadriceps and hamstrings.

4. Rheumatoid arthritis, psoriatic arthritis, SLE.
5. Acute monoarticular arthritis—septic arthritis, disseminated gonorrhea, gout, pseudogout, rheumatic fever, seronegative spondyloarthropathy, Lyme disease.
6. Osteochondritis dissecans (OCD)—an area of necrotic bone and degenerative changes in the overlying cartilage. The bone/cartilage piece may separate from the underlying bone and become a loose body in the joint, causing symptoms of pain, catching, and popping. Treatment options are limited but arthroscopic surgery can help. If the loose fragment is in the joint, arthroscopic removal of fragment is indicated.
7. Iliotibial (IT) band syndrome—pain over the lateral knee (where the IT band attaches to the proximal tibia), primarily in runners and cyclists.
8. Osgood–Schlatter disease in adolescents—resolves with skeletal maturity.

Quick HIT

Recurrent knee effusion is a sign of intra-articular pathology and further investigation is warranted.

9. Baker cyst—caused by intra-articular pathology (e.g., meniscus tear).
   a. Rupture can cause pain/swelling, and if it extends into the calf, may mimic thrombophlebitis or acute deep venous thrombosis.
   b. Majority resolves spontaneously.
10. Patellar tendinitis (“jumper’s knee”)
    a. Common cause of anterior knee pain (at inferior pole of patella).
    b. Running and jumping sports—an “overuse” injury.
    c. Treatment is activity modification and quadriceps/hamstring rehabilitation (stretching/strengthening program).

11. Plica syndrome—a diagnosis of exclusion, typically seen in athletes or with overuse injuries, sometimes after trauma. MRI and examination findings are unreliable. Patients have pain along the medial patella and a feeling of snapping of the knee with walking, with or without intermittent effusion. Treatment is conservative (physical therapy), anti-inflammatory medications, steroid injections. If conservative treatment fails, arthroscopic release of plica can be helpful.

B. Diagnosis

1. Radiographs—if degenerative disease is suspected or if there is a history of trauma or acute injury.
2. MRI—if any ligamentous instability is apparent or a meniscal tear is suspected.
3. Knee aspiration ("tap")—use this for analysis of synovial fluid if septic joint is suspected. In general, synovial fluid examination is recommended for monoarticular joint swelling. It may relieve symptoms.

Quick HIT

By following the Ottawa ankle rules, unnecessary radiographs of the ankle are avoided and clinically significant fractures are not missed.

Ankle Sprains

A. General Characteristics

1. The lateral side of the ankle consists of three ligaments: anterior talofibular ligament (ATFL), calcaneofibular ligament (CFL), and posterior talofibular ligament. The ATFL is most commonly injured
2. The medial side ligaments (deltoid ligaments) are typically not injured in a classic inversion ankle sprain
3. Classification into three grades is based on severity
   a. Grade 1: partial rupture of ATFL
   b. Grade 2: complete rupture of ATFL and partial rupture of CFL
   c. Grade 3: complete rupture of both ATFL and CFL

Quick HIT

Treatment of all acute ankle sprains (even severe sprains) involves RICE and physical therapy. Surgery is rarely, if ever, needed acutely. Recurrent ankle sprains, however, require evaluation for possible surgery.

B. Diagnosis

1. Patients typically have tenderness directly over the injured ligament. ATFL is located just at the anterior tip of the distal fibula.
2. Ankle radiographs are not necessary if the following conditions are met (Ottawa ankle rules):
   a. Patient is able to walk four steps at the time of injury and at the time of evaluation.
   b. There is no bony tenderness over distal 6 cm of either malleolus.
   c. There is no bony tenderness at the base of 5th metatarsal or navicular bone.

Quick HIT

Impingement Syndrome

- Common cause of shoulder pain
- Due to impingement of greater tuberosity on acromion
- Pain with overhead activity
- May lead to rotator cuff pathology over time
- Steroid injections offer temporary relief
- Surgery (acromioplasty) is very effective

C. Treatment

1. Rest, ice, compression, elevation (RICE) in the acute period, then controlled pain-free range-of-motion exercises with gradual return to weight bearing.
2. Physical therapy after the acute phase of swelling has subsided to regain full range of motion, strength, and proprioception. Physical therapy involves peroneal tendon strengthening and proprioceptive training.
3. Surgery is rarely necessary acutely, even for grade 3 sprains.

4. Chronic ankle instability (recurrent ankle sprains) needs further evaluation by an orthopedic surgeon.

Tendinitis and Bursitis

A. Tendinitis

1. Supraspinatus (rotator cuff) tendinitis—impingement syndrome.
   a. Most common cause of shoulder pain.
   b. Pain occurs subacromially and on the lateral aspect of the shoulder with arm abduction; pain is poorly localized (difficult for patient to pinpoint) with an insidious onset. It is generally located over the lateral deltoid.
   c. This is seen in elderly patients (degeneration of tendons) and in young patients who do a lot of overhand lifting/throwing (sports or work related).
   d. Pain may be referred to the lateral arm.
   e. If weakness is present on shoulder abduction, a rotator cuff tear should be suspected. (MRI is the best test for diagnosis of rotator cuff tear.)
   f. Treatment: physical therapy (strengthen shoulder musculature), subacromial steroid injection. Arthroscopic surgery is helpful if conservative treatment fails.
2. Lateral epicondylitis at the elbow ("tennis elbow").
   a. Caused by inflammation/degeneration of the extensor tendons of the forearm, which originates from the lateral epicondyle; results from excessive/repetitive supination/pronation.
   b. Splinting the forearm (counterforce brace) is the initial treatment (do not splint or wrap the elbow itself).
   c. Physical therapy is often helpful—strengthening/stretching extensors of forearm. This, along with activity modification, typically leads to resolution of pain.
   d. Injections only if physical therapy fails. Surgery is effective but only used if all conservative measures have been exhausted. Surgery is rarely necessary for this condition.
3. Medial epicondylitis at the elbow ("golfer's elbow").

a. Pain distal to medial epicondyle (origin of flexor muscles of the forearm).
b. Exacerbated by wrist flexion; caused by overuse of the flexor pronator muscle group. Treatment similar to lateral epicondylitis (physical therapy, activity modification).

Quick HIT

Hip osteoarthritis presents with groin pain. Lateral hip pain (over the greater trochanter) or in the buttock region is not due to osteoarthritis. Before diagnosing osteoarthritis of the hip as source of pain, make certain patient's symptoms are primarily in the groin.

4. De Quervain tenosynovitis
   a. Pain at the radial aspect of the wrist (especially with pinch gripping) in region of radial styloid; common for pain to radiate to elbow or into thumb.
   b. Due to inflammation of the abductor pollicis longus and extensor pollicis brevis tendons.
   c. Positive Finkelstein test—have the patient clench the thumb under the other fingers when making a fist. Then ulnarly deviate the wrist. The test is positive if pain is reproduced.
   d. Treatment is thumb spica splint and NSAIDs. Local cortisone injections can be helpful. Surgery done if conservative measures fail and is usually effective.

Quick HIT

Differential diagnosis of hand numbness (as seen in carpal tunnel syndrome):
- Cervical radiculopathy (nerve root compression in the cervical spine)
- Peripheral neuropathy (diabetes)
- Median nerve compression in forearm

B. Bursitis

1. Olecranon bursitis—swelling (and perhaps pain) at point of elbow; spongy "bag of fluid" over olecranon (due to effusion into the olecranon bursa).

a. Treatment is conservative.
b. If infection is suspected, drainage may be necessary.

2. Trochanteric bursitis—this is a very common cause of lateral hip pain. The greater trochanter is exquisitely painful on palpation.
   a. Causes include trauma, overuse injury, weakness of hip musculature. In many cases, no inciting event is present and the onset is insidious.
   b. Treatment is NSAIDs and activity modification. If symptoms persist, local cortisone injections into the bursa are very effective in providing relief.

Quick HIT

A negative Phalen test or Tinel sign does not exclude carpal tunnel syndrome.

Carpal Tunnel Syndrome

A. General Characteristics

1. Caused by **median nerve compression** within the tight confines of the carpal tunnel, causing numbness and pain in median nerve distribution. If long standing and severe, atrophy of thenar muscles may be seen.
2. Associated conditions include hypothyroidism, diabetes, repetitive use of hands in certain activities, pregnancy, recent trauma, or fracture of the wrist.

B. Clinical Features

1. Numbness, pain, or tingling in the **median nerve distribution**—usually worse at night; sometimes patient has pain/numbness along the entire arm (as far as the shoulder).
2. Muscle weakness and thenar atrophy may develop later.

C. Diagnosis

1. Physical examination
   a. **Tinel sign**—tap over median nerve at wrist crease; causes paresthesias in median nerve distribution

b. **Phalen test**—palmar flexion of the wrist for 1 minute; causes paresthesias in median nerve distribution

2. Electromyography (EMG) and nerve conduction velocity (NCV) study
   a. For definitive diagnosis
   b. Indicated if diagnosis is not clear from clinical findings or if patient develops weakness or persistent symptoms

D. Treatment

1. Wrist splints (volar carpal splint) should be worn at night during sleep. The purpose is to prevent wrist flexion during sleep (which compresses the nerve).
2. Anti-inflammatory medications (NSAIDs).
3. Local corticosteroid injection—relief can be long term in some patients.
4. Surgical release is very effective. Consider this option for patients who have persistent symptoms or if the symptoms are limiting the patient's activities or quality of life.

Osteoarthritis

A. General Characteristics

1. Osteoarthritis (OA) is characterized by **degeneration of cartilage** (due to wear and tear) and by hypertrophy of bone at the articular margins.
2. By the age of 65 years, more than 75% of the population has radiographic evidence of osteoarthritis in weight-bearing joints (hips, knees, lumbar spine).
3. Any joint can be affected, but weight-bearing joints are most commonly involved (hips, knees, cervical, and lumbar spine).

B. Risk Factors

1. Age
2. Obesity
3. Excessive joint loading (manual labor, athletes, etc.)
4. Trauma
   a. Repeated microtrauma—in many cases, a patient's occupation or athletic activities requires repetitive motions (such as repeated knee

bending) that predispose the patient to degenerative joint disease in later years
   b. Macrotrauma (fractures, ligament injuries)—intra-articular fractures can cause OA
5. Genetic predisposition
6. Altered joint anatomy or instability (developmental hip dysplasia, dislocation due to trauma, rheumatoid arthritis, gout, pseudogout)
7. Deposition diseases cause chondrocyte injury, or make the cartilage stiffer (hemochromatosis, ochronosis, alkaptonuria, Wilson disease, Gaucher disease, gout, CPPD)
8. Hemophilia (hemarthroses)

Quick HIT

The following can contribute to or exacerbate forces to the cartilage:
- Compromised pain sensation or proprioception
- Ligamental laxity
- Falls of very short distances (because they do not provide ample opportunity for compensatory movements to decrease the impact load)

C. Clinical Features

1. Joint pain (often monoarticular)
   a. This is caused by movement of one joint surface against another (bone on bone) because of cartilage loss. There are no pain fibers in cartilage, so its insidious destruction over time goes unnoticed. Once it is completely worn out, the bones (which do have pain fibers) start rubbing against each other, producing the pain of osteoarthritis
   b. Deep, dull ache that is relieved with rest and worsened with activity
   c. Insidious onset, with gradual progression over many years
2. Stiffness in the morning or after a period of inactivity (Note: morning stiffness lasting >30 minutes may suggest an inflammatory arthritis such as rheumatoid arthritis)
3. Limited range of motion (late stages) due to bony enlargement of joints (osteophytes); bony crepitus may be present
4. No systemic symptoms; no erythema or warmth. Swelling may be present and suggests inflammation

Quick HIT

If the spine is involved, nerve roots may become compressed and lead to radicular pain.

Quick HIT

Hip osteoarthritis causes pain in the groin (not lateral hip or buttock). If patient is tender over the lateral aspect of hip, suspect greater trochanteric bursitis.

D. Diagnosis

1. Plain radiographs are the initial tests and should be obtained in all patients suspected of having osteoarthritis (Figure 12-5). Ideally, radiographs should be obtained in the standing position (for lower extremities). Findings include:
   a. **Joint space narrowing** (due to loss of cartilage)—key finding on radiographs
   b. **Osteophytes**
   c. **Sclerosis** of subchondral bony end plates adjacent to diseased cartilage—most severe at points of maximum pressure
   d. **Subchondral cysts**—occur as a result of increased transmission of intra-articular pressure to the subchondral bone
2. All blood tests are normal
3. MRI of the spine if indicated (neurologic findings, before surgery)

Quick HIT

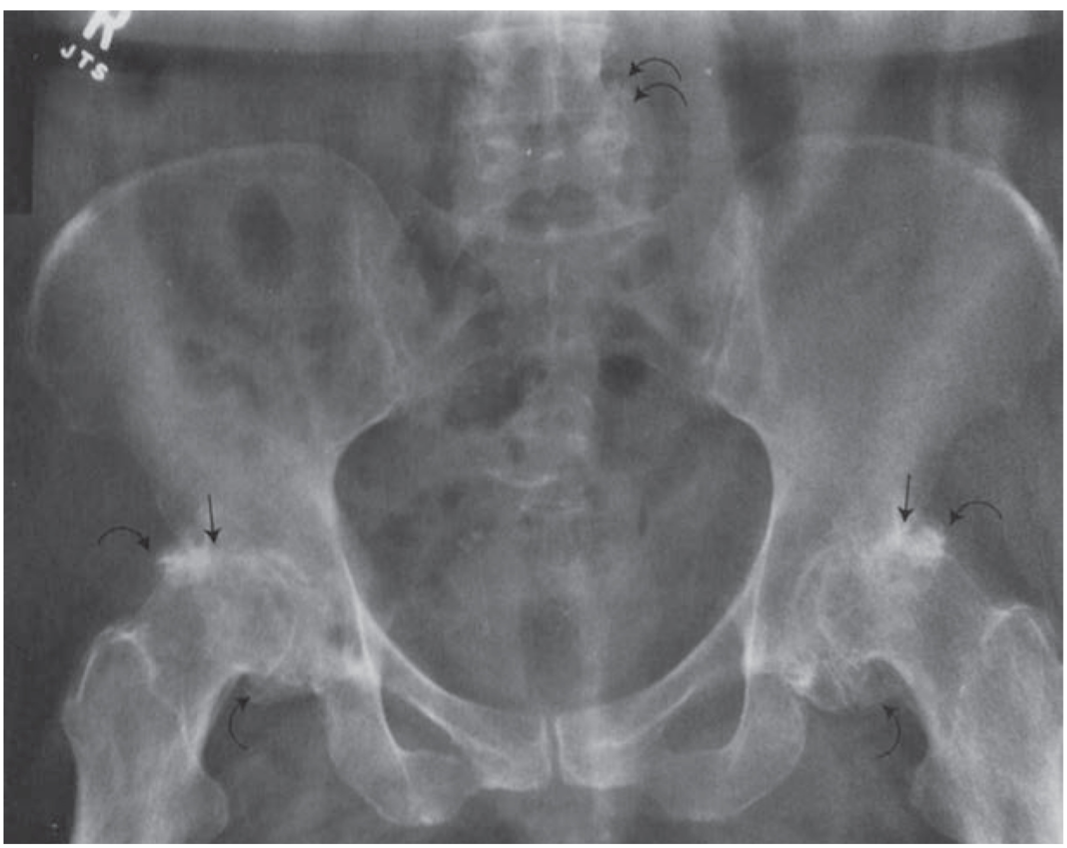
Radiographic findings in osteoarthritis: joint space narrowing, osteophytes, subchondral sclerosis, subchondral cysts.

E. Treatment

1. Nonpharmacologic treatment
   a. Avoid activities that involve excessive use of the joint
   b. Weight loss is very important

c. Physical therapy can be beneficial. Goals are to maintain range of motion and muscle strength. Swimming is an ideal exercise (involves minimal involvement of weight-bearing joints); avoid excessive walking
d. Use canes or crutches to reduce weight on the joint

A



B

FIGURE 12-5 **A: Right knee AP radiograph showing osteoarthritis. Note medial joint space narrowing, osteophyte formation (*curved arrow*), and irregular articular surfaces (*straight arrow*). B: Pelvic AP radiograph. Bilateral osteoarthritis of the hip. Note narrowing of hip joint spaces, osteophytes (*curved arrows*), and osteophytes in the lumbar spine (*double curved arrows*). Also note subchondral cysts and sclerosis of the femoral heads.**
(**A** reprinted with permission from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Lippincott-Raven; 1998:287. Figure 11–72; **B** reprinted with permission from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Lippincott-Raven; 1998:288. Figure 11–73A.)

2. Pharmacologic treatment
   a. Acetaminophen is the first-line agent.
   b. NSAIDs are just as effective as acetaminophen (but GI bleeding is a concern with long-term use). Of selective COX-2 inhibitors, only celecoxib remains on the market but is rarely used. All the others have been removed from the market due to increased risk of cardiovascular events. Main benefit of selective COX-2 inhibitors is a decrease in gastric/duodenal ulcers and a decrease in GI symptoms, with the same (not superior) analgesic and anti-inflammatory effects of the nonselective NSAIDs.
   c. Intra-articular injections of corticosteroids are very helpful, but more than three to four injections per year is not recommended. Patients may have up to 3 months of pain relief with each injection. In elderly patients with severe OA who are not good surgical candidates for joint replacement, more frequent injections are justified if it provides good pain control.
   d. Viscosupplementation—hyaluronic acid is injected into the knee joint and augments the viscoelastic properties of normal synovial fluid. Recent studies show good pain relief, but results are variable.
3. Surgery for serious disability
   a. Total joint replacement may be performed if conservative therapy fails to control pain. It should be delayed as long as possible because

a revision may be needed 15 to 20 years after surgery. Total hip and knee replacements are among the most successful procedures in orthopedics with reliable pain relief.

4. Nutritional products—glucosamine and chondroitin sulfate
   a. Over-the-counter products that many patients claim to improve arthritis symptoms, although high-quality randomized trials have not shown any meaningful benefit.

Quick HIT

With osteoarthritis of the hips, the pain is in the **groin region** and sometimes radiates to the anterior thigh.

Quick HIT

For **left** knee or hip pain, the cane should be held in the **right** hand.

Quick HIT

Although x-rays are diagnostic of OA, not all patients with x-ray findings of OA have symptoms. There is no consistent correlation between symptoms and severity of x-ray findings.

Quick HIT

It is often difficult to differentiate between primary and secondary osteoporosis, and the two may coexist. It is best to attempt to identify any predisposing conditions and eliminate them if possible.

Osteoporosis

A. General Characteristics

1. Decreased bone mass/quality causes increased bone fragility and fracture risk. In osteoporosis, the bone mineral density is at least 2.5

standard deviations below that of young, normal individuals

2. Mechanism: failure to attain optimal (peak) bone mass before age 30 years, or rate of bone resorption exceeds rate of bone formation after peak bone mass is attained
3. Most osteoporotic patients are postmenopausal women and elderly men
4. Classification
   a. Primary osteoporosis
      - Type I (most often in postmenopausal women 51 to 75 years of age)—excess loss of trabecular bone; vertebral compression fractures and Colles fractures are common
      - Type II (most often in men and women over 70 years of age)—equal loss of both cortical and trabecular bone; fractures of femoral neck, proximal humerus, and pelvis most common

   b. Secondary osteoporosis—an obvious cause is present, such as excess steroid therapy/Cushing syndrome, immobilization, hyperthyroidism, long-term heparin, hypogonadism in men, and vitamin D deficiency

Quick HIT

Some elderly patients have progressive kyphosis (hunchback deformity) because they have multiple vertebral compression fractures.

Quick HIT

Osteoporosis is a “silent” disease. It is asymptomatic until a fracture occurs.

Quick HIT

An exercise program along with calcium and vitamin D supplementation is the mainstay of the therapy for prevention or treatment of osteoporosis.

Quick HIT

The **PROOF trial** showed the following regarding **calcitonin:**

- No effect at hip
- Shown to decrease risk of vertebral fractures by as much as 40%
- Slight increase in bone density at lumbar vertebrae

B. Risk Factors

1. Estrogen depletion
   a. Postmenopausal state—all women are estrogen deficient after menopause; however, osteoporosis does not develop in all women
   b. History of athletic amenorrhea, eating disorders, oligomenorrhea
   c. Early menopause
2. Female gender—women have a lower peak bone mass and smaller vertebral end plates
3. Calcium deficiency/vitamin D deficiency
4. Decreased peak bone mass
5. Heritable risk factors—family history, European or Asian ancestry, thin/slight build
6. Decreased physical activity (prolonged immobility)
7. Endocrine—hypogonadism in men (with low testosterone), hyperthyroidism (see Clinical Pearl 12-9)
8. Smoking and alcohol abuse
9. Medications—corticosteroids, prolonged heparin use

CLINICAL PEARL 12-9

Osteoporotic Fracture Risk Assessment

Validated risk factors for osteoporotic fracture risk that are independent of bone mineral density are:

- Advanced age
- Previous osteoporotic fracture
- Long-term steroid therapy
- Cigarette smoking
- Low body weight (<58 kg)
- Family history of hip fracture
- Excess alcohol intake
- Rheumatoid arthritis
- Secondary osteoporosis

Quick HIT

Recommend the following to all patients with osteoporosis:

- Daily calcium
- Daily vitamin D
- Weight-bearing exercise
- Smoking cessation

C. Clinical Features

1. Vertebral body compression fractures (of the middle and lower thoracic and upper lumbar spine) are the most common. Very rare in cervical spine
   a. Result in pain and deformity, including kyphosis
   b. Severe back pain after minor trauma
   c. Restricted spinal movement, loss of height
2. Colles fracture (distal radius fracture)—usually due to fall on outstretched hand; more common in postmenopausal women
3. Hip fractures—femoral neck, intertrochanteric fractures
4. Increased incidence of long bone fractures—humerus, femur, tibia

Quick HIT

Of all fragility fractures, hip fractures have highest morbidity and mortality.

D. Diagnosis

1. DEXA (dual-energy x-ray absorptiometry) scan is the gold standard
   a. Very precise for measuring bone density
   b. Indications for bone mineral density measurement:
      - All women aged 65 years and older
      - Postmenopausal women <65 years with one or more risk factors for fracture.
      - Men with risk factors for fracture
   c. Sites selected are femoral neck and lumbar spine. Compare the density of bone with a standard control, which is the bone density of a healthy 30-year-old person
   d. Can range from normal to osteopenia to osteoporosis. T-scores are used according to WHO classification (see Table 12-6)
      - WHO classification (T-scores) are used in all postmenopausal and perimenopausal women, and in men over age 50 years. In all other patients (including premenopausal women), z-scores are used
2. Rule out secondary causes—check calcium, phosphorus, alkaline phosphatase, TSH, vitamin D, free PTH, creatinine, CBC

Quick HIT

Unfortunately, many patients with fragility fractures do not subsequently receive osteoporosis therapy, despite data showing a beneficial effect in reducing the risk of a second fracture.

TABLE 12-6 Bone Mineral Density T-Score Criteria for Osteopenia and Osteoporosis

Diagnosis	T-Score
Normal	Greater than or equal to 1.0
Osteopenia	Between −1.0 and −2.5
Osteoporosis	Less than or equal to −2.5
Severe osteoporosis	Less than or equal to −2.5 and fragility fracture

Adapted from World Health Organization, http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf

E. Treatment

1. Nonpharmacologic therapy
   a. Diet—adequate calorie intake, avoid malnutrition
      - Supplemental elemental calcium (1,200 mg/day)
      - 800 international units of vitamin D daily
   b. Exercise—weight-bearing exercise for 30 minutes, at least 3 times a week, to stimulate bone formation
   c. Smoking cessation is critical—smoking accelerates bone loss
   d. Eliminate or reduce alcohol intake
2. Pharmacologic therapy
   a. Indicated in the following patients:
      - Postmenopausal women with established osteoporosis (T-score −2.5 or less) or fragility fracture (hip or vertebral)
      - High-risk postmenopausal women with osteopenia (T-score between −1.0 and −2.5)
   b. Bisphosphonates inhibit bone resorption and are first-line treatment
      - They decrease osteoclastic activity (via binding to hydroxyapatite) and decrease the risk of fractures
      - Oral bisphosphonates (alendronate, risedronate) are preferred in most patients
      - Side effects include reflux, esophageal irritation, and ulceration
      - If patient cannot tolerate oral bisphosphonates, use IV bisphosphonates (IV zoledronic acid)

c. PTH therapy or human recombinant PTH therapy
   - PTH is an effective drug that increases bone mineral density and reduces fracture risk. Due to high cost, subcutaneous administration, and long-term safety concerns, it is not a first-line drug
   - Indicated in patients with severe osteoporosis (T-score less than −2.5) who cannot tolerate bisphosphonates, or who continue to fracture despite being on bisphosphonates for 1 year
   - Maximum duration of treatment is 24 months, because of concern for osteosarcomas, which have been observed in rats. After stopping PTH, can restart bisphosphonates

d. Denosumab is a monoclonal antibody directed at RANKL, which acts to reduce the activity of osteoclasts

e. Selective estrogen receptor modulators (SERMs), such as tamoxifen or raloxifene, inhibit bone resorption and reduce the risk of fractures

f. Romosozumab is a monoclonal antibody that inhibits sclerostin, and was recently approved by the FDA after data showing it reduces the risk of fracture. However it is not a first-line agent

g. Calcitonin or estrogen-progestin therapy is no longer recommended

Quick HIT

Most common causes of visual impairment/loss in developed countries:
- Diabetic retinopathy (most common cause in adults <65 years)
- ARMD (most common cause in adults >65 years)
- Cataracts
- Glaucoma

Diseases of the Eye

Age-Related Macular Degeneration

- Most common cause of vision loss in people over 65 years of age in developed countries.

- Age-related macular degeneration (ARMD) is characterized by loss of central vision (because the macula is affected). Blurred vision, distortion, and scotoma are common. Complete loss of vision almost never occurs. Peripheral vision is preserved.
- The main risk factor is advanced age. Other risk factors are female gender, Caucasian race, smoking, HTN, and family history.
- Two categories: exudative (“wet”) and nonexudative (“dry”) macular degeneration.
- Exudative ARMD causes sudden visual loss due to leakage of serous fluid and blood as a result of abnormal vessel formation (neovascularization) under the retina.
- Nonexudative ARMD is characterized by atrophy and degeneration of the central retina. Yellowish-white deposits called **drusen** form under the pigment epithelium and can be seen with an ophthalmoscope.
- Intraocular injections of medications (anti-VEGF inhibitors) have supplanted laser photocoagulation and other therapies for wet ARMD.
- Over-the-counter formulations of vitamins are recommended for dry and wet ARMD.

***Quick* HIT**

Age-Related Macular Degeneration

- The “wet” form of ARMD can develop at any time, so patients with “dry” ARMD must be monitored closely.
- Supplements of certain vitamins containing antioxidants are thought to be beneficial, but a preventative or therapeutic effect has not been proven.
- **Ranibizumab (and several other related drugs), given as repeated intraocular injections,** have been shown to be effective in treating “wet” ARMD.

Glaucoma

A. General Characteristics

1. Glaucoma is **one of the most important causes of blindness worldwide.** It is a complex disease typically characterized by increased IOP, damage to the optic nerve, and irreversible vision loss.

2. The pathogenesis of optic nerve damage in glaucoma is not fully understood. Ischemia may play a major role. Over time, there is a loss of ganglion cells, leading to atrophy of the optic disc and enlargement of the optic cup, called "**cupping.**"
3. There are many types of glaucoma, but they generally fall into the following two categories:
   a. Open-angle glaucoma—accounts for 90% of all cases
      - Characterized by impaired outflow of aqueous humor from the eye.
      - Absence of symptoms early in the course can lead to delay in diagnosis and "silent" progression.

   b. Closed-angle glaucoma
      - Acute angle-closure glaucoma—characterized by very rapid increase in IOP due to occlusion of **the anterior chamber angle (between the cornea and the iris where the trabecular meshwork is located)** and obstruction of outflow of aqueous humor.
      - **This is an ophthalmologic emergency that can lead to irreversible vision loss within hours if untreated.**
      - May be precipitated by dilation of the iris in a patient with a pre-existing anatomically narrow anterior chamber angle.

B. Risk Factors

1. Older age (over 50 years)
2. African-American race (increased incidence of open-angle glaucoma)
3. Asian or Eskimo ancestry (increased incidence of acute angle-closure glaucoma)
4. Family history of glaucoma
5. History of significant eye trauma or intraocular inflammation
6. Steroid medications

Quick HIT

Patients with acute angle-closure glaucoma may have severe abdominal pain and nausea, and they are occasionally misdiagnosed as having an acute surgical abdomen (e.g., appendicitis).

C. Clinical Features

1. Open-angle glaucoma
   a. Painless, increased IOP (may be the only sign), characteristic changes in optic nerve
   b. Progressive and insidious visual field loss (usually sparing central vision until end-stage disease)
2. Closed-angle glaucoma
   a. Red, painful eye
   b. Sudden decrease in visual acuity (blurred vision), seeing “halos,” markedly elevated IOP
   c. Nausea and vomiting (common), headache
   d. Involved pupil is dilated and nonreactive (in mid-dilation)

D. Diagnosis

1. Tonometry measures IOP; should be performed regularly in patients with or at risk for glaucoma.
2. Ophthalmoscopy—evaluate the optic nerve for glaucomatous damage.
3. Gonioscopy is used to visualize the anterior chamber and helps determine the cause of glaucoma. It requires skill to perform.
4. Visual field testing should be performed in all patients in whom glaucoma is suspected and regularly in everyone with glaucoma to monitor disease progression.
5. Imaging (OCT) of the optic nerve also is helpful in assessing and monitoring progression of axonal loss of the optic nerve in glaucoma patients.

Quick HIT

The goal of treatment is to control IOP, and thereby prevent further optic nerve and visual field loss.

E. Treatment

1. Chronic open-angle glaucoma (in escalating order)
   a. Topical medications—most patients are first treated topically with a β-blocker, α-agonist, carbonic anhydrase inhibitor, and/or prostaglandin analogue by themselves or in combination to reach the target pressure.
   b. Laser or surgical treatment for refractory cases.
2. Acute angle-closure glaucoma
   a. An ophthalmic emergency—refer to an ophthalmologist immediately. Emergently lower the IOP. Medical treatment includes timolol, brimonidine, dorzolamide, pilocarpine, and/or prednisolone drops. Can give IV acetazolamide and oral mannitol if IOP is still elevated after previous measures.
   b. Laser or surgical iridectomy is a definitive treatment.

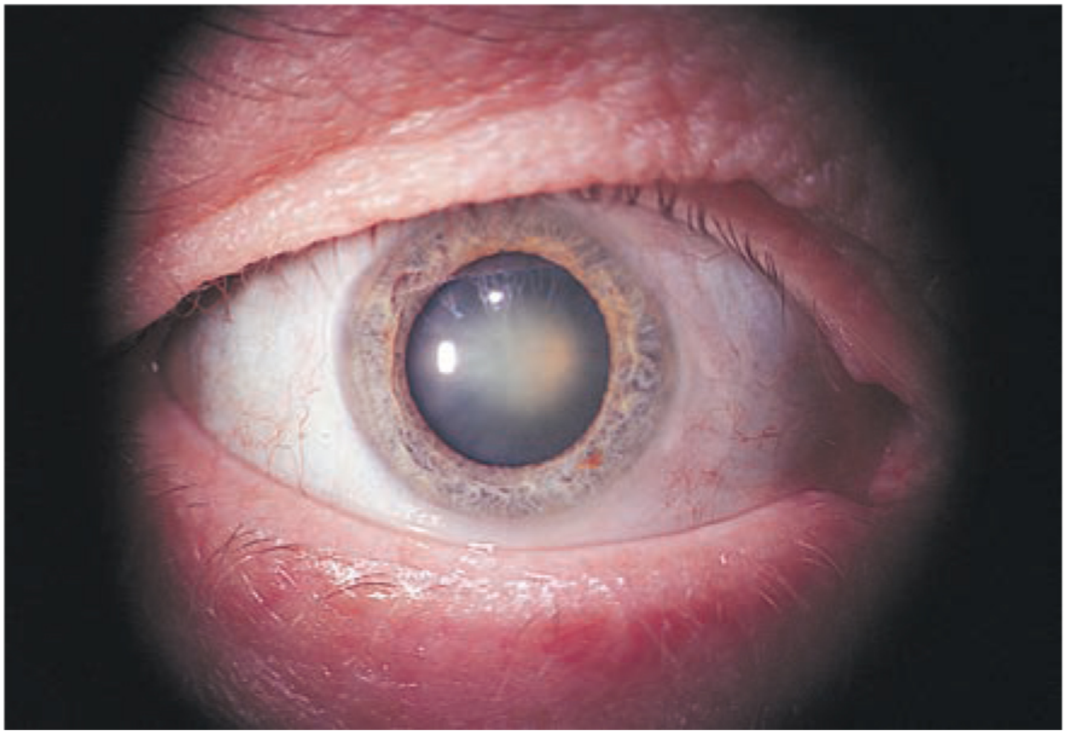


FIGURE 12-6 **Cataract.**
(Reprinted with permission from Tasman W, Jaeger EA. *The Wills Eye Hospital Atlas of Clinical Ophthalmology*. 2nd ed. Lippincott Williams & Wilkins; 2001. Figure 12-2.)

Cataracts

- Opacifications of the natural lens of the eye: **half of people over age 75 years have cataracts** (Figure 12-6).
- There is a **loss of visual acuity** that progresses slowly over many years. Patients may complain of glare and difficulty driving at night.
- Risk factors include old age, cigarette smoking, glucocorticoid use, prolonged UV radiation exposure, trauma, diabetes, Wilson disease, Down syndrome, and certain metabolic diseases.
- Surgery is the definitive treatment and is very effective in restoring vision. It is indicated if visual loss is significant to the patient and interferes with daily or occupational activities. It involves extraction of the cataract with implantation of an artificial intraocular lens.

Quick HIT

"Second Sight"

- Some patients with cataracts become increasingly near-sighted and may no longer require reading glasses. This is referred to as "second sight."
- This phenomenon is due to the cataract increasing the refractive power of the lens of the eye.

Red Eye

A. General Characteristics

1. Many causes of red eye are benign, but the initial goal in evaluation should be to identify conditions that require (emergent or nonemergent) referral to an ophthalmologist.
2. Conjunctivitis is the most common cause of red eye, but always attempt to exclude other, more serious causes.
3. The following conditions require a referral to an ophthalmologist:
   a. Eye pain that does not respond to therapy.
   b. Flashers, floaters, or a sudden decrease in visual acuity.
   c. History of recent eye surgery—especially if infection is suspected.
   d. Corneal opacification, corneal ulcer, or corneal foreign body that cannot be removed.
   e. History of penetrating trauma or significant blunt trauma.
   f. History of chemical exposure (especially alkali agents).
   g. Orbital cellulitis.
   h. Presence of hypopyon or ciliary flush (suggests acute glaucoma, corneal inflammation, or iridocyclitis).
   i. Asymmetric or unreactive pupils.
4. Always check visual acuity, pupil size, and reactivity. Evert lids to look for a foreign body.

Quick HIT

In general, steroid eye drops should only be administered by an ophthalmologist.

B. Differential Diagnosis

1. Conjunctivitis—see below
2. Subconjunctival hemorrhage
   a. Caused by rupture of small conjunctival vessels; induced by Valsalva maneuver trauma or, less commonly, coagulopathies or HTN
   b. Causes focal unilateral blotchy redness of the conjunctiva (looks worse than it is)
   c. Usually self-limiting and resolves in a few weeks
3. Keratoconjunctivitis sicca (dry eye)
   a. Very long differential diagnosis, including medications (e.g., anticholinergics or antihistamines), autoimmune diseases (e.g., Sjögren's), CN V or VII lesions
   b. The eye may appear normal, or may be mildly injected
   c. Patients may complain of a foreign-body sensation
   d. Treat with artificial tears during the day. Consider a lubricating ointment at night. Many other treatments are available
4. Acute angle-closure glaucoma (see above)—consult an ophthalmologist immediately
5. Blepharitis
   a. Inflammation of the eyelid; often associated with infection with *Staphylococcus* spp.
   b. Usually diagnosed by careful examination of the eyelid margins, which are red and often swollen with crusting that sticks to the lashes
   c. Treat with lid scrubs and warm compresses. Give topical antibiotics for severe cases
6. Episcleritis
   a. Inflammation of vessels lining the episclera (the lining just beneath the conjunctiva)
   b. Thought to be an autoimmune process—may be seen with connective tissue diseases, but usually idiopathic
   c. Causes redness, irritation, dull ache, and possible watery discharge
   d. The sclera may appear blotchy with areas of redness over the episcleral vessels
   e. Usually self-limiting; NSAIDs may provide symptomatic relief
   f. Refer the patient for evaluation by an ophthalmologist

7. Scleritis
   a. Inflammation of the sclera is associated with systemic immunologic disease, such as rheumatoid arthritis
   b. It causes significant eye pain (severe, deep pain). On examination, there is ocular redness and pain on palpation of the eyeball. It can cause visual impairment
   c. Refer the patient for prompt evaluation by an ophthalmologist. Treatment involves topical and sometimes systemic corticosteroids
8. Acute anterior uveitis (also known as iritis or iridocyclitis)
   a. Inflammation of the iris and ciliary body; more common in the young and middle-aged
   b. Associated with connective tissue diseases (e.g., sarcoidosis, ankylosing spondylitis, Reiter syndrome, and IBD)
   c. Clinical findings: ciliary flush (redness most prominent around the cornea), blurred vision, pain and photophobia; constricted pupil compared with contralateral eye
   d. Refer the patient for prompt evaluation by an ophthalmologist
9. Herpes simplex keratitis
   a. Caused by HSV-1; may present similarly to viral conjunctivitis, except usually unilateral
   b. Presents with ocular irritation and photophobia. Pain may be absent
   c. Look for classic **dendritic ulcer on the cornea; can result in irreversible vision loss if untreated**
   d. Warrants semiurgent ophthalmology referral
   e. Treat with topical antiviral eye drops or ganciclovir gel. Consider oral acyclovir or valcylovir for those who cannot tolerate or administer topical therapy

Quick HIT

Viral conjunctivitis is highly contagious! Patients should avoid any direct or indirect eye contact with others. Encourage strict personal hygiene and frequent handwashing. Clean all surfaces and equipment in contact with the patient as soon as the patient leaves the office.

Quick HIT

When a patient presents with red and itchy eyes, tearing, and nasal congestion, think allergic conjunctivitis.

Conjunctivitis

A. General Characteristics

1. Conjunctivitis is the most common cause of red eye.
2. Conjunctivitis generally refers to inflammation of the transparent membrane that lines the inside of the eyelids (palpebral conjunctiva) and the globe (bulbar conjunctiva).

CLINICAL PEARL 12-10

Do Not Send a Patient Home Who Has a Rapid Onset of Copious, Purulent Exudate!

- This is consistent with **hyperacute bacterial conjunctivitis,** caused by *Neisseria gonorrhoeae.*
- The typical patient is a sexually active young adult.
- Symptoms progress rapidly to severe redness, swelling, and pain.
- **This warrants immediate attention from an ophthalmologist.**
- If untreated, it can lead to corneal scarring and blindness.

Quick HIT

Wearing contact lenses overnight dramatically increases a person's risk for developing corneal infection and ulceration.

B. Causes

1. Viral conjunctivitis (see also Clinical Pearl 12-10).

a. The **most common** form of conjunctivitis. Adenovirus is the most common organism.
b. Inquire about a recent history of URI.
c. Hyperemia of one or both eyes, usually one eye followed by spread to the other in a few days is common. Watery discharge is frequently present.
d. A palpable preauricular lymph node may be present.
e. It is usually self-limited, but some patients develop membranous conjunctivitis that requires topical steroids and stripping of the membranes.

2. Bacterial conjunctivitis (Figure 12-7)
   a. Most commonly caused by *S. aureus* in adults, though other common organisms include *S. pneumoniae, H. influenzae,* and *M. catarrhalis.*
   b. Rapid onset of irritation, hyperemia, and tearing.
   c. Characterized by a mucopurulent exudate with crusting.
3. Chlamydial conjunctivitis—two important forms.
   a. Trachoma (caused by *Chlamydia trachomatis* serotypes A, B, and C)
      - Most common cause of blindness worldwide due to chronic scarring.
   b. Inclusion conjunctivitis (*C. trachomatis* serotypes D to K).
      - Mainly transmitted by genital-hand-eye contact in patients with sexually transmitted infection (STI).
4. Allergic conjunctivitis.
   a. Very common in patients with atopic disease; usually seasonal.
   b. It is typically characterized by redness, itching, tearing, and nasal conjunctivitis. Eyelid edema may also be present. It is typically bilateral.
5. Conjunctivitis secondary to irritants (e.g., contact lenses, chemicals, foreign bodies, dryness).

C. Treatment

1. Viral conjunctivitis: cold compress, strict hand washing; topical antibiotics if bacterial superinfection is suspected
2. Bacterial conjunctivitis

   a. Acute—use broad-spectrum topical antibiotics (e.g., erythromycin, ciprofloxacin, sulfacetamide). Therapy can be altered based on culture results
   b. Hyperacute—treat gonococcal conjunctivitis with a one-time dose of ceftriaxone, 1 g IM, as well as topical therapy.
3. Chlamydial conjunctivitis
   a. Adults and adolescents—oral tetracycline, doxycycline, or erythromycin for 2 weeks
   b. Treat sexual partner(s) for STI
4. Allergic conjunctivitis
   a. Remove the allergen, if possible. Advise the use of cold compresses
   b. Treat with topical antihistamines or mast cell stabilizers
   c. Systemic antihistamines can be effective as well
   d. Topical NSAIDs may be a useful adjunct to treatment

Amaurosis Fugax

- Some variability with how this is defined, but generally refers to sudden, transient loss of vision in one or both eyes
- Causes of transient monocular vision loss include carotid artery disease (cholesterol plaque embolization), cardioembolic phenomenon, giant cell (temporal) arteritis, and others
- Order carotid ultrasonography and cardiac workup (e.g., lipid profile, ECG)

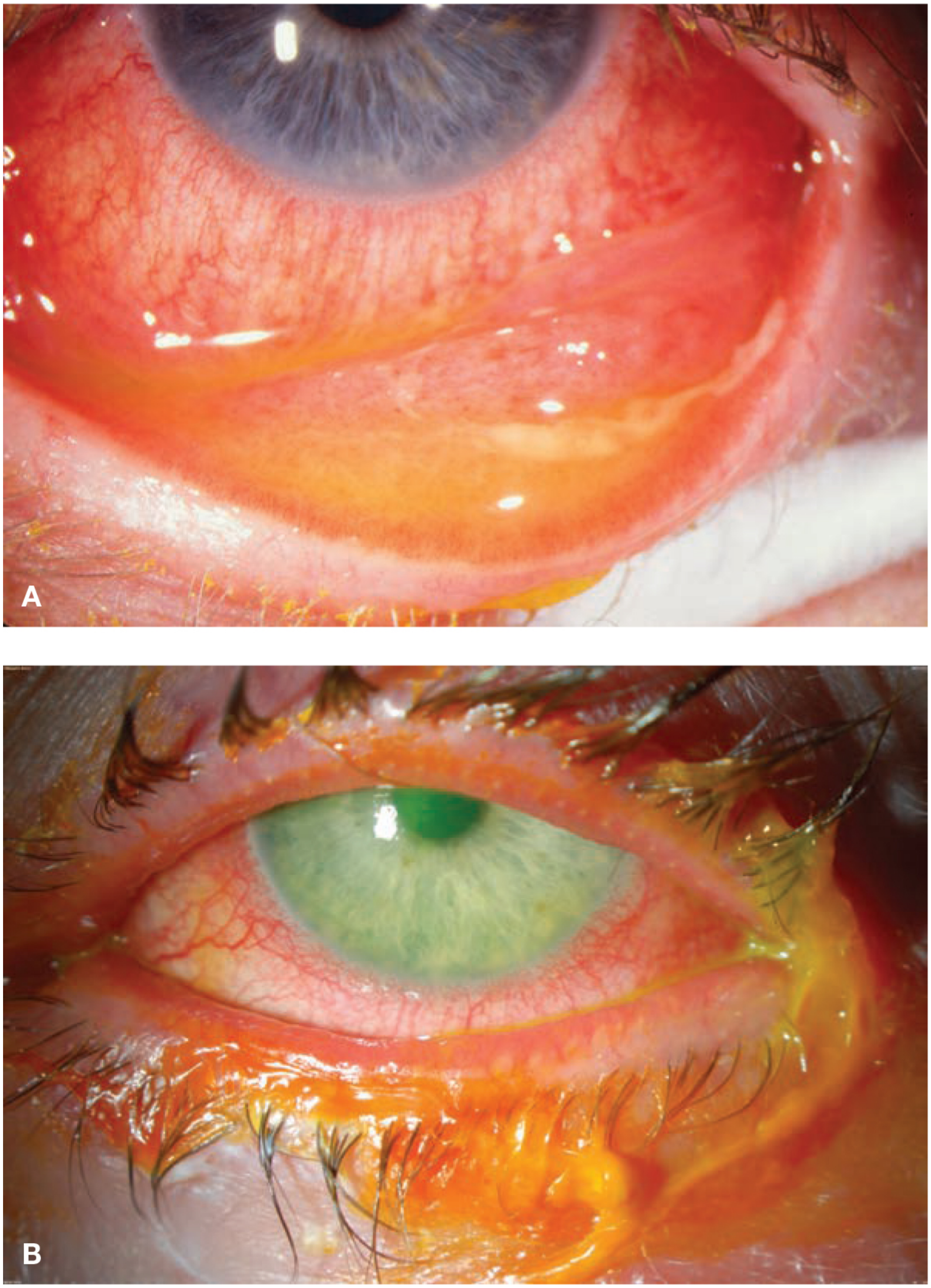


FIGURE 12-7 Bacterial conjunctivitis.
(Reprinted with permission from Rapuano CJ. *Cornea*. 3rd ed. Wolters Kluwer; 2018. Figure 1-3A.)

Sleep Disorders

Obstructive Sleep Apnea

A. General Characteristics

1. Intermittent obstruction of the air flow (typically at the level of the oropharynx) produces periods of apnea during sleep.
2. Each apneic period is usually 20 to 30 seconds long (but may be longer) and results in hypoxia, which arouses the patient from sleep. This occurs multiple (sometimes hundreds of) times overnight.

B. Risk Factors

1. Obesity (especially around the neck)—although nonobese patients can also have OSA
2. Structural abnormalities—enlarged tonsils, uvula, soft palate; nasal polyps; hypertrophy of muscles in the pharynx; deviated septum; deep overbite with small chin
3. Family history
4. Alcohol and sedatives worsen the condition
5. Hypothyroidism (multifactorial)

C. Clinical Features

1. Snoring
2. Daytime sleepiness due to disrupted nocturnal sleep
3. Personality changes, decreased intellectual function, decreased libido
4. Repeated oxygen desaturation and hypoxemia can lead to systemic and pulmonary HTN as well as cardiac arrhythmias
5. Other features: morning headaches, polycythemia

D. Diagnosis

Polysomnography (overnight sleep study in a sleep laboratory) confirms the diagnosis.

E. Treatment

1. All patients should undergo behavior modification, which includes weight loss and exercise, avoiding alcohol and sedatives, and sleeping in a nonsupine position
2. Mild-to-moderate OSA
   a. Should be offered positive airway pressure therapy
   b. If patient refuses or there are issues with compliance, an oral appliance can be offered

Quick HIT

Complications of OSA

- Increased pulmonary vascular resistance (due to hypoxemia); over time, can lead to pulmonary HTN and eventually cor pulmonale (more likely if the patient is obese)
- Systemic HTN (due to increase in sympathetic tone)

3. Severe OSA
   a. **Continuous positive airway pressure** provides positive pressure, thus preventing occlusion of the upper pharynx. This is the preferred therapy for the majority of patients because it is noninvasive and has proven efficacy. It is poorly tolerated by some due to noise and discomfort
   b. Alternative therapies include surgery of the upper airway or oral appliances

Narcolepsy

A. Inherited disorder (of variable penetrance) of REM sleep regulation (i.e., REM sleep involuntarily occurs at random and inappropriate times)

B. Results in **excessive sleepiness** during the day

C. Characterized by the following features:

1. Involuntary "sleep attacks" at any time of day (during any activity, including driving) that last several minutes
2. Cataplexy, which is loss of muscle tone that generally occurs with an intense emotional stimulus (e.g., laughter, anger)
3. Sleep paralysis, in which patient cannot move when waking up
4. Hypnagogic hallucinations that are vivid (visual or auditory) —"dreams" while awake

D. The disorder can range from mild to severe

E. Automobile accidents are a major problem

F. Treatment: modafinil (use is supported by RCTs), methylphenidate (Ritalin), or amphetamines; planned naps during the day may prevent sleep attacks

> ***Quick* HIT**
>
> Questions to ask the patient with insomnia—sleep history, timing of insomnia, sleep habits

Insomnia

A. Causes

1. Acute or transient insomnia is usually due to psychological stress or travel over time zones ("jet lag")

2. Chronic causes
   a. Secondary insomnia accounts for over 90% of all cases
      - Psychiatric conditions—depression, anxiety disorders, posttraumatic stress disorder, manic phase of bipolar disorder, schizophrenia, obsessive-compulsive disorder
      - Medications and substance abuse—alcohol, sedatives (with prolonged use, patients develop tolerance and withdrawal rebound insomnia), caffeine, β-blockers, stimulant drugs (amphetamines), decongestants, some SSRIs, nicotine
      - Medical problems—advanced COPD, renal failure, CHF, chronic pain
      - Other—fibromyalgia, chronic fatigue syndrome (CFS)
   b. Primary insomnia is a diagnosis of exclusion. DSM-5 defines it as dissatisfaction with sleep and one of the following: difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakenings and a subsequent inability to fall back asleep
      - By definition, it is nonrestorative sleep that occurs three nights per week for at least 3 months in the absence of other medical, psychiatric, or sleep disorders, and that causes clinically significant distress and social or occupational impairment
      - Patients worry excessively about not falling asleep and become preoccupied with it. The cause is unknown

B. Treatment

1. Treat the underlying cause, if found.
2. Consider a psychiatric evaluation if psychiatric causes or primary insomnia are suspected.
3. Use sedative–hypnotic medications sparingly and with caution for symptomatic relief. Use the smallest dose possible, and avoid use for longer than 2 to 3 weeks.

Miscellaneous Topics

Obesity

A. General

1. Considered to be a global epidemic, particularly in developed nations
2. Health hazards associated with obesity: HTN, heart disease, hyperlipidemia, type 2 diabetes, stroke, osteoarthritis, liver disease, cancer, OSA, obesity hypoventilation syndrome, and depression
3. Obesity is associated with a significant increase in mortality
4. Body Mass Index (BMI) = weight divided by height squared (kg/m^2)
   a. Underweight: BMI less than 18.5
   b. Normal: 18.5 to 24.9
   c. Overweight: 25 to 29.9
   d. Obese: 30 and over
      - Obesity class I: 30 to 34.9
      - Obesity class II: 35 to 39.9
      - Obesity class III: 40 and over

B. Treatment

1. Diet, exercise, and lifestyle modification are mainstays of treatment.
2. Drug therapy—for patients who have not succeeded in losing weight with diet and exercise. GLP-1 antagonists (e.g., liraglutide), orlistat, and others can be tried.
3. Bariatric surgery
   a. Bariatric surgery is effective in reducing comorbidities associated with obesity, including HTN, diabetes, OSA, and hyperlipidemia. This translates into a 29% reduction in mortality. Only indicated in patients who have earnestly tried other means of losing weight and have been unsuccessful.
   b. Best evidence is for patients with BMI over 40.
   c. Bariatric surgery is based on two mechanisms: restriction of intake (via a small stomach reservoir) and malabsorption (via decreasing small bowel length). Restrictive techniques are technically easier,

have lower complication rates, but result in less weight loss than malabsorptive techniques.

d. Most common procedure is the laparoscopic Roux-en-Y gastric bypass. The laparoscopic adjustable gastric banding (LapBand) has fewer complications, is reversible, but is not as effective in achieving weight loss as compared with the gastric bypass.

Hearing Loss/Impaired Hearing

A. General Characteristics—two types of hearing loss

1. Conductive hearing loss
   a. **Caused by lesions in the external or middle ear**
   b. Due to interference with mechanical reception or amplification of sound, which occurs with disease of the auditory canal, tympanic membrane, or ossicles
2. Sensorineural hearing loss—due to lesions in the cochlea or CN VIII (auditory branch)

Quick HIT

Tympanic Membrane Perforation

- History: pain, conductive hearing loss, tinnitus
- Examination: bleeding from the ear, clot in the meatus, visible tear in the tympanic membrane
- Ninety percent heal spontaneously within 6 weeks. Surgery is appropriate for larger perforations.

B. Causes

1. Conductive hearing loss
   a. External canal
      - Cerumen impaction—buildup obstructs the auditory canal (most common cause)
      - Otitis externa
      - Exostoses—bony outgrowths of external auditory canal related to repetitive exposure to cold water (e.g., scuba divers, swimmers)

b. Tympanic membrane perforation

- Usually due to trauma (direct or indirect)
- May be secondary to middle ear infection

c. Middle ear

- Any cause of middle ear effusion (fluid in middle ear interferes with sound conduction)—otitis media, allergic rhinitis
- Otosclerosis—bony fusion (immobilization) of the stapes to the oval window; an autosomal dominant condition (variable penetrance); corrected with surgery; rarely progresses to deafness
- Other—neoplasms, congenital malformation of the middle ear

Quick HIT

Hearing Impairment

- History: medications; history of head trauma, infection (otitis media, otitis externa); noise exposure (occupational or recreational)
- Physical examination: inspect auditory canal (impacted cerumen, exostoses); examine tympanic membrane (inflammation, perforation, scarring); assess middle ear (fluid)

2. Sensorineural hearing loss

a. Presbycusis (most common cause)

- Gradual, symmetric hearing loss associated with aging—most common cause of diminished hearing in elderly patients
- Pathology—degeneration of sensory cells and nerve fibers at the base of the cochlea
- Hearing loss is most noticeable at high frequencies with slow progression to lower frequencies

b. Noise-induced hearing loss

- Chronic, prolonged exposure to sound levels >85 dB
- Hair cells in the organ of Corti are damaged

c. Infection—viral or bacterial infection of cochlear structures or labyrinth

d. Drug-induced hearing loss

- Aminoglycoside antibiotics, furosemide, ethacrynic acid; cisplatin, quinidine

- Aspirin can cause tinnitus and reversible hearing impairment

e. Injury to inner ear or cochlear nerve (e.g., skull fracture)
f. Congenital (TORCH infections)
g. Ménière disease

- Fluctuating, unilateral hearing loss
- Sensorineural hearing loss, sense of pressure/fullness in ear, tinnitus, vertigo
- Vertigo usually responds to dietary salt restriction and meclizine, but hearing loss is progressive

h. CNS causes—acoustic neuromas, meningitis, auditory nerve neuritis (multiple sclerosis, syphilis), meningioma

C. Clinical Features

1. Conductive hearing loss
   a. Decreased perception of sound (especially for low-frequency sounds)
   b. Can hear loud noises well
2. Sensorineural hearing loss
   a. Difficulty hearing loud noises; shouting may exacerbate the problem (annoyed by loud speech)
   b. Can hear sounds, but has trouble deciphering words (poor speech discrimination)
   c. More difficulty with high-frequency sounds (doorbells, phones, child's voice, female voice)
   d. Tinnitus is often present

D. Diagnosis

1. Whisper test—ask the patient to repeat words whispered into the tested ear (mask the other ear) (see Clinical Pearl 12-11)
2. An audiogram is an essential component of the evaluation
3. MRI—in selected cases (e.g., if CNS tumor or multiple sclerosis is suspected)

CLINICAL PEARL 12-11

Rinne and Weber Tests

- Conductive loss
  - Abnormal Rinne test—bone conduction is better than air conduction
  - Weber—**sound lateralizes to the affected side** (tuning fork is perceived more loudly in the ear with a conductive hearing loss)
- Sensorineural loss
  - Normal Rinne test—air conduction is better than bone conduction
  - Weber—**sound lateralizes to the unaffected side**

E. Treatment

1. Cerumen impaction is best treated by irrigation after several days of softening with carbamide peroxide (Debrox) or triethanolamine (Cerumenex)
2. Conductive hearing loss
   a. Treat underlying cause
   b. Surgical techniques such as tympanoplasty (reconstructs middle ear) for patients with chronic otitis media; stapedectomy for otosclerosis
   c. Hearing aids
3. Sensorineural hearing loss
   a. Treat underlying cause
   b. Hearing aids
   c. Cochlear implants—transduce sounds to electrical energy, stimulates CN VIII

Quick HIT

The most common cause of incontinence in elderly patients is urge incontinence. In women <**70 years** of age, the most common cause is stress incontinence.

Urinary Incontinence

A. General Characteristics

1. There are five major types of incontinence (urge, stress, overflow, functional, and mixed). Many patients have more than one type.
2. Male incontinence is usually due to BPH or neurologic disease. A urology evaluation is indicated for incontinent male patients.
3. Female incontinence is usually due to hormonal changes, pelvic floor dysfunction or laxity, or uninhibited bladder contractions (detrusor contractions) secondary to aging.

> ***Quick* HIT**
>
> **Evaluating a Patient with Urinary Incontinence**
>
> Inquire about the history of diabetes, multiple sclerosis, Parkinson disease, stroke, spinal cord injury or disease, and pelvic surgery.

B. Risk Factors

1. Age—diminished size of bladder, earlier detrusor contractions, postmenopausal genitourinary atrophy
2. Recurrent urinary tract infections
3. Immobility, decreased mental status, dementia, stroke, Parkinson disease, depression
4. DM, CHF
5. Multiparity, history of prolonged labor
6. Pelvic floor dysfunction in women, BPH and prostate cancer in men
7. Medications
   a. Diuretics increase bladder filling, increasing the episodes of incontinence
   b. Anticholinergics and adrenergics cause urinary retention
   c. β-Blockers diminish sphincter tone
   d. Calcium channel blockers and narcotics can decrease detrusor contraction
   e. Alcohol, sedatives, hypnotics (depress mentation)

Quick HIT

- If urgency of urination is the prominent finding, suspect urge incontinence.
- If increased intra-abdominal pressure (cough, laugh) causes urine loss, suspect stress incontinence.

Quick HIT

Elderly women commonly have both urge and stress incontinence.

C. Types of Urinary Incontinence

1. Urge incontinence (also called detrusor instability)
   a. Most common type in elderly and nursing-home patients
   b. Multiple causes (often idiopathic), including dementia, stroke, severe illness, Parkinson disease
   c. Mechanism: involuntary and uninhibited detrusor contractions result in involuntary loss of urine
   d. Clinical features: sudden urge to urinate (e.g., patients are unable to make it to the bathroom), a loss of large volumes of urine with small postvoid residual, and nocturnal wetting
   e. Diagnostic study of choice is urodynamic study
   f. Management is initially with bladder-training exercises (the goal being to increase the amount of time between voiding). If this is unsuccessful, medications include anticholinergics (oxybutynin) and TCAs (imipramine)
2. Stress incontinence
   a. Occurs mostly in women (after multiple deliveries of children)
   b. Mechanism: Weakness of the pelvic diaphragm (pelvic floor) leads to loss of bladder support (with resultant hypermobility of the bladder neck). This causes the proximal urethra to descend below the pelvic floor so that an increase in intra-abdominal pressure is transmitted mostly to the bladder (instead of an equal transmission to the bladder and urethra)
   c. Clinical features: involuntary urine loss (only in spurts) during activities that increase intra-abdominal pressure (cough, laugh,

sneeze, exercise); small postvoid volume

d. Rule out infection with a urinalysis

e. Management: Kegel exercises (multiple contractions of pelvic floor muscles as if the patient were interrupting flow of urine) to strengthen pelvic floor musculature; estrogen replacement therapy; use of a pessary; surgery (there are various options, and a popular option is the midurethral sling)

3. Overflow incontinence
   a. Common in diabetic patients and patients with neurologic disorders
   b. Mechanism: Inadequate bladder contraction (due to impaired detrusor contractility) or a bladder outlet obstruction leads to urinary retention and subsequent overdistention of the bladder. Bladder pressure increases until it exceeds urethral resistance, and then urine leakage occurs
   c. Causes: neurogenic bladder (diabetic patients, lower motor neuron lesions), medications (anticholinergics, α-agonists, and epidural/spinal anesthetics), **obstruction to urine flow** (BPH, prostate cancer, urethral strictures, severe constipation with fecal impaction)
   d. Clinical features: nocturnal wetting, frequent loss of small amount of urine; large postvoid residual (usually exceeds 100 mL)
   e. Management (primarily medical): intermittent self-catheterization is the best management; cholinergic agents (e.g., bethanechol) to increase bladder contractions; α-blockers (e.g., terazosin, doxazosin) to decrease sphincter resistance
4. Functional incontinence—secondary to disabling and debilitating diseases

Quick HIT

Laboratory studies in workup of fatigue:

- CBC (anemia)
- TSH (hypothyroidism)
- Fasting glucose (diabetes mellitus)
- BMP (electrolyte abnormalities)
- Urinalysis, BUN/creatinine (renal disease)
- LFT (liver disease)

D. Diagnosis

1. Urinalysis (all patients)—to exclude infection and hematuria
2. Postvoid urine catheterization—record the residual volume. Normal residual volume is less than 50 mL. A urine volume greater than 50 mL may indicate urinary obstruction or a hypotonic bladder
3. Urine cultures—if dysuria and positive urinalysis (WBCs in urine)
4. Renal function studies (BUN/Cr), glucose levels
5. Voiding record is useful—time, volume of episodes, record of oral intake, medications, associated activities
6. Perform further testing in carefully selected patients in whom the cause is not identified. Tests include cystometry, uroflow measurement/urethral pressure profile, imaging studies such as intravenous pyelogram, and voiding cystourethrogram, as needed

Fatigue

A. General Characteristics

1. Fatigue refers to a lack of energy or a sense of being tired—differentiate this from muscular weakness. It is not directly related to exertion
2. Differential diagnosis
   a. Psychiatric causes—depression (most common cause); anxiety and somatization
   b. Endocrine causes—hypothyroidism, poorly controlled DM, apathetic hyperthyroidism of elderly patients, Addison disease, hypopituitarism, hyperparathyroidism, and other causes of hypercalcemia
   c. Hematologic/oncologic causes—severe anemia, occult malignancy (e.g., pancreatic carcinoma)
   d. Metabolic causes—chronic renal failure, hepatocellular failure
   e. Infectious diseases—mononucleosis, viral hepatitis, HIV, syphilis, hepatitis B and C, CMV, parasitic disease, tuberculosis and subacute bacterial endocarditis, Lyme disease
   f. Cardiopulmonary disease—OSA, CHF
   g. Medications—antihypertensive medications (clonidine, methyldopa), antidepressants (amitriptyline, doxepin, trazodone are

more sedating), hypnotics, β-blockers, antihistamines, drug abuse/withdrawal

h. Other causes: CFS, fibromyalgia, sleep disturbances (sleep apnea, narcolepsy, insomnia)

Quick HIT

Etiology of Chronic Fatigue

- Only 5% of cases are diagnosed as CFS.
- Most cases of chronic fatigue are due to depression, anxiety, or both (up to two-thirds of cases).
- Between 20% and 25% of cases are idiopathic, yet do not fit the criteria for CFS.
- Less than 5% are due to an unidentified medical illness.

3. CFS
   a. CFS is profound fatigue for longer than 6 months that is not due to a medical or psychiatric disorder. More common in women
   b. Cause is unknown. A flu-like illness may act as the triggering event, but infection has not been established as the proven cause. Other theories point to immunologic disturbance or endocrine dysfunction as possible causes
   c. CFS is a diagnosis of exclusion—rule out other causes before making a diagnosis of CFS
   d. Most patients experience partial recovery within 2 years, but relapses can occur at any time
   e. There are specific criteria for diagnosis. The key features include:
      - New or definite onset of unexplained fatigue, not alleviated by rest, not due to exertion, and significantly affecting quality of life
      - Four or more of the following symptoms (for at least 6 months): diminished short-term memory or concentration, muscle pain, sore throat, tender lymph nodes, unrefreshing sleep, joint pain (without redness/swelling), headaches, postexertional malaise for longer than 24 hours
   f. Depression is common in patients with CFS

B. Diagnosis

1. Basic laboratory tests to exclude other causes—consider CBC, LFTs, serum electrolytes, calcium, TSH, erythrocyte sedimentation rate, and HIV testing (if indicated).
2. Extensive testing other than the above is not indicated.

C. Treatment

1. Treat the underlying disorder, if known
2. Treat CFS and patients with idiopathic fatigue as follows:
   a. Cognitive behavioral therapy, including exercise, social, and psychological behavior modifications
   b. Antidepressants, as appropriate
   c. NSAIDs for relief of headache, arthralgias

Erectile Dysfunction

A. General Characteristics

1. Erectile dysfunction is the recurring inability to achieve and maintain an erection sufficient for satisfactory sexual performance.
2. It is thought that up to half of all men in the United States between the ages of 40 and 70 have some form of erectile dysfunction. Prevalence increases with age.
3. Pathophysiology—once thought to be psychogenic in origin, it is now known that most cases (80%) are organic. A normal erection is largely dependent on the healthy penile and systemic vasculature.
4. Some cases of erectile dysfunction are psychogenic.

B. Risk Factors

1. The most important risk factors are those that contribute to atherosclerosis (e.g., HTN, smoking, hyperlipidemia, diabetes)
2. Medications—antihypertensives (may indirectly lower intracavernosal pressure by virtue of lowering systemic BP)
3. Hematologic—sickle cell disease
4. History of pelvic surgery or perineal trauma
5. Alcohol abuse

6. Any cause of hypogonadism/low testosterone state, including hypothyroidism
7. Congenital penile curvature

C. Diagnosis

1. Detailed history and examination, including a digital rectal examination and neurologic examination. Assess for signs of PAD.
2. Laboratory tests—obtain a CBC, chemistry panel, fasting glucose, and lipid profile. If there is hypogonadism or loss of libido, order serum testosterone, prolactin levels, and thyroid profile.
3. Nocturnal penile tumescence—if normal erections occur during sleep, a psychogenic cause is likely. If not, the cause is probably organic.
4. Consider vascular testing—evaluate arterial inflow and venous trapping of blood. Tests include intracavernosal injection of vasoactive substances, duplex ultrasound, and arteriography.
5. Psychological testing may be appropriate in some cases.

D. Treatment

1. Treat the underlying cause. Address atherosclerotic risk factors.
2. First-line treatment is with phosphodiesterase inhibitors such as sildenafil citrate (Viagra), which acts by increasing cGMP levels, causing increased nitric oxide release and penile smooth muscle relaxation. It can be taken 30 to 60 minutes before anticipated intercourse. It is contraindicated with use of nitrates because together they can cause profound hypotension.
3. Intracavernosal injections of vasoactive agents (patient learns to self-administer).
4. Vacuum constriction devices are rings placed around the base of the penis that enhance venous trapping of blood; they may interfere with ejaculation.
5. Psychological therapy may be indicated to reduce performance anxiety and address underlying factors that may be causing or contributing to erectile dysfunction.
6. Hormonal replacement (e.g., testosterone) in patients with documented hypogonadism.
7. Penile implants for patients who have not responded to the above.

Addiction Medicine

Overview of Substance Use Disorders (SUDs)

1. SUDs are very common, and up to 15% of the US population over 12 years old met criteria in the past year.
2. All SUDs (alcohol use disorder, opioid use disorder, stimulant use disorder, etc.) are diagnosed using the DSM-5 criteria, which also specify the severity of the SUD.
3. There is a strong genetic component to addiction, and an increased likelihood of developing an SUD in patients that experience more adverse childhood events (ACEs).
4. Early screening for SUDs is very important and can be accomplished in a variety of healthcare and community settings. SBIRT (Screening, Brief Intervention, and Referral to Treatment) is a common method to screen for the presence and severity of an SUD, to provide education and motivational interviewing for change, and to refer to an appropriate treatment center.

Quick HIT

Diagnosis of substance use disorders and their severity is based on the DSM-5 criteria.

5. Screening for comorbid mental health conditions is important, since SUD + mental health ("dual diagnosis") is very common.
6. While there are FDA-approved medications for alcohol and opioid use disorders, there is no FDA-approved medication to treat stimulant use disorder (e.g., cocaine, methamphetamine).

Each beverage portrayed above represents one standard drink (or one alcohol drink equivalent), defined in the United States as any beverage containing .6 fl oz or 14 grams of pure alcohol. The percentage of pure alcohol, expressed here as alcohol by volume (alc/vol), varies within and across beverage types. Although the standard drink amounts are helpful for following health guidelines, they may not reflect customary serving sizes.

FIGURE 12-8 Definition of a standard drink.
(Reprinted with permission from Arcangelo VP, Peterson AM, Wilbur V, et al. *Pharmacotherapeutics for Advanced Practice: A Practical Approach*. 5th ed. Wolters Kluwer; 2021:873.)

Alcohol Use Disorder

A. General Characteristics

1. Heavy drinking: the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has defined heavy, or "risky" drinking, as an amount that puts patients at risk for health consequences and developing a use disorder. For males under the age of 65 years, this is >14 drinks in a week or >4 drinks in a day. For females (and males >65 years old), this is >7 drinks in a week or >3 drinks in a day. See Figure 12-8.
2. There are a variety of screening questionnaires for alcohol use disorder, including the AUDIT-C, CAGE, and single item-screening.
   a. CAGE (Any more than one positive answer may suggest alcohol abuse)
      - **C**ut down? (Have you ever felt the need to cut down on your drinking?)
      - **A**nnoyed? (Have you ever felt annoyed by criticisms of your drinking?)

- **G**uilty? (Have you ever felt guilty about drinking?)
- **E**ye-opener? (Have you ever felt the need to have a drink first thing in the morning?)

***Quick* HIT**

Laboratory Findings in Alcohol Use Disorder

- Anemia
- Macrocytic (most common)—due to folate deficiency
- Microcytic—due to GI bleeding
- LFTs—increased GGT; AST–ALT ratio is 2:1
- Hypertriglyceridemia
- Hyperuricemia, hypocalcemia
- Thiamine deficiency
- Decreased testosterone level

B. Complications

1. GI—gastritis, esophagitis, PUD, alcoholic liver disease (alcoholic hepatitis, cirrhosis, portal HTN), pancreatitis (acute and chronic), Mallory–Weiss tears
2. Cardiac—alcoholic cardiomyopathy, essential HTN (more than three drinks per day significantly increases BP)
3. CNS
   a. **Wernicke encephalopathy**—often reversible
      - Caused by thiamine deficiency
      - Manifests as nystagmus, ataxia, ophthalmoplegia, confusion
      - Can be precipitated by administering glucose in alcoholics without first giving thiamine replacement

   b. **Korsakoff psychosis**—irreversible
      - Caused by thiamine deficiency
      - Alcohol-induced amnestic disorder
      - Mostly affects short-term memory; confabulation is common
4. Pulmonary—pneumonia, aspiration
5. Nutritional deficiencies (vitamins, minerals)—especially thiamine deficiency, hypomagnesemia, and folate deficiency
6. Peripheral neuropathy—due to thiamine deficiency
7. Sexual dysfunction—impotence, loss of libido

8. Psychiatric—depression, anxiety, insomnia
9. Increased risk of malignancy—esophagus, oral, liver, lung
10. Frequent falls, minor injuries, **motor vehicle accidents**

CLINICAL PEARL 12-12

Alcohol Withdrawal

- Features include tachycardia, sweating, anxiety, hallucinations.
- Goal is to prevent progression to delirium tremens (DT), which is a medical emergency (mortality rate, 20%). DT occurs in 5% of alcoholic withdrawals.
- DT is delirium developing within a week of the last alcohol intake, usually 2 to 4 days after the last drink. DT is characterized by tactile hallucinations, visual hallucinations, confusion, sweating, and autonomic instability manifesting as tachycardia and hypertension.

C. Treatment

1. Alcohol withdrawal can be lethal, so high-risk patients should be monitored during withdrawal in a medical setting (Clinical Pearl 12-12)
2. Benzodiazepines are the most commonly used medications to treat withdrawal. Barbiturates such as phenobarbital are also often used (alone, synergistically with benzodiazepines, or as a loading dose in the emergency department)
3. Symptom-triggered therapy (as opposed to fixed-dose therapy) using a validated scoring system such as CIWA or MINDS, reduces length of stay and total benzodiazepine use
4. Treatment of alcohol use disorder
5. Peer support groups, including Alcoholics Anonymous (AA)
6. Treatment programs: there is no perfect treatment for every patient, thus treatment should be individualized based on patient-specific factors. There is a wide spectrum of treatment options, including inpatient and residential programs, intensive outpatient, and individual counseling
7. Medication-assisted treatment (MAT)

8. There are three FDA-approved medications: naltrexone, acamprosate, and disulfiram.
9. Naltrexone is a good first-line option that reduces the cravings for alcohol. It can't be used in the setting of significantly elevated liver enzymes or concomitant opioid use
10. Acamprosate is another option to reduce cravings, but must be taken three times daily. It can be used with liver dysfunction, but should be avoided in significant renal impairment
11. Disulfiram works by inhibiting aldehyde dehydrogenase, leading to an accumulation of acetaldehyde which will make patients feel very sick. There is not a lot of data showing a benefit of this medication, but it can be appropriate in supervised settings. It should be avoided in patients with significant cardiovascular disease (e.g., CAD, heart failure)

***Quick* HIT**

Naltrexone, acamprosate, and disulfiram are FDA-approved treatments for alcohol use disorder. Methadone, buprenorphine, and naltrexone are FDA-approved treatments for opioid use disorder. There are no FDA-approved treatments for stimulant use disorder.

Opioid Use Disorder

A. Overview

1. The incidence of opioid use disorder has increased dramatically since the 1990s. From 1999 to 2019, ~500,000 people have died from an opioid overdose (including both prescription and illicit opioids).
2. The rise of synthetic opioids such as fentanyl has contributed to a rise in overdose deaths.
3. There are effective treatment options for opioid use disorder, with many large studies showing a reduced risk of overdose and death. However, these treatments are often underutilized, due to lack of provider awareness and bias toward this patient population.

B. Diagnosis

1. Diagnosis of opioid use disorder is based on the DSM 5 criteria
2. Diagnosis and severity assessment of opioid withdrawal is based on a scoring system, such as Clinical Opiate Withdrawal Scale (COWS):
   a. COWS relies on a combination of subjective (e.g., bone/joint aches, anxiety/irritability) and objective findings (e.g., tachycardia, dilated pupils, yawning during assessment) that helps rate the opioid withdrawal severity as mild, moderate, or severe.

C. Treatment

1. All patients should be assessed for opioid dependence, the severity of their use disorder, and linked to treatment. Most patients with a moderate-to-severe use disorder should be treated with a combination of pharmacotherapy and psychotherapy. However, the treatment plan for each patient should be individualized: whereas daily treatment with methadone at an opioid treatment program should be pursued for some patients, harm reduction strategies such as clean needle exchange may be most appropriate for precontemplative patients. Naloxone should be given to patients given the high rates of opioid overdose.
2. For patients with opioid dependence, opioid agonists such as methadone and buprenorphine should be started to treat withdrawal and as maintenance therapy.
   a. Opioid agonists are not "trading one addiction for another." Patients that are maintained on opioid agonists maintain opioid tolerance (which reduces the risk of overdose and death), are more likely to stay in treatment, and are less likely to use illicit opioids. In some studies, methadone treatment reduces all-cause mortality by as much as 50%.
   b. Buprenorphine is a partial agonist with a high affinity for opioid receptors, thus the patient must be experiencing opioid withdrawal prior to starting. If given too early, it can precipitate withdrawal symptoms. See Figure 12-9.
   c. Methadone can prolong the QTc, so an ECG should be checked if the patient has cardiac risk factors or is on other QTc-prolonging medications.

3. Naltrexone is an opioid antagonist that blocks the effects of opioids, which reinforces abstinence. It cannot be given to opioid dependent patients, since it will cause immediate opioid withdrawal.

Smoking

A. Health Risks Associated With Cigarette Smoking

1. Cardiovascular disease—CAD, acute MI, and stroke; there is a dose-dependent relationship between smoking and cardiovascular disease
2. COPD risk increases with smoking in a dose-dependent manner
3. Malignancy—smoking increases the risk of lung cancer, head and neck cancer, GI cancers (laryngeal/pharyngeal, esophageal, gastric, pancreatic, hepatic, colorectal), GU cancers (renal, ureter, bladder, penile, cervical), and myeloid leukemia
4. PUD
5. Osteoporosis—decreases peak bone mass and increases the rate of bone loss
6. Premature skin aging
7. PAD, Buerger disease
8. Adverse effects during pregnancy—smoking increases the risk of spontaneous abortion, fetal death, neonatal death, sudden infant death syndrome, and low birth weight
9. Infections, especially respiratory

Quick HIT

Most important causes of smoking-related mortality are lung cancer, COPD, and ASCVD.

Quick HIT

Behavioral modification is crucial for long-term smoking cessation. The patch or gum should be used in conjunction with a smoking withdrawal clinic (behavioral program). Quit rates are higher with this combination.

B. Smoking Cessation

1. Varenicline—partial agonist at the α-4–β-2 subunit of the nicotinic acetylcholine receptor. Its efficacy has been demonstrated in several randomized controlled trials. Considered first-line therapy. See Figure 12-9.
2. Nicotine replacement therapy.
   a. Both a long-acting agent (nicotine patch) and a short-acting agent (nicotine gum or lozenge) should be used together for higher quit rates.
   b. Nicotine patch.
      - Quit rates are 2.5 times higher at 6 months than with placebo.
      - Continuous nicotine delivery weans the patient from nicotine, and the dose is gradually decreased. There are no peaks or troughs as associated with smoking, so it eliminates nicotine withdrawal symptoms.
      - The dose of nicotine in the patch is based on how many cigarettes the patient is smoking, and the dose of the patch is gradually reduced over weeks.
   c. Nicotine chewing gum, lozenge, inhaler, or nasal spray.
      - These are used for breakthrough cravings on top of the patch.

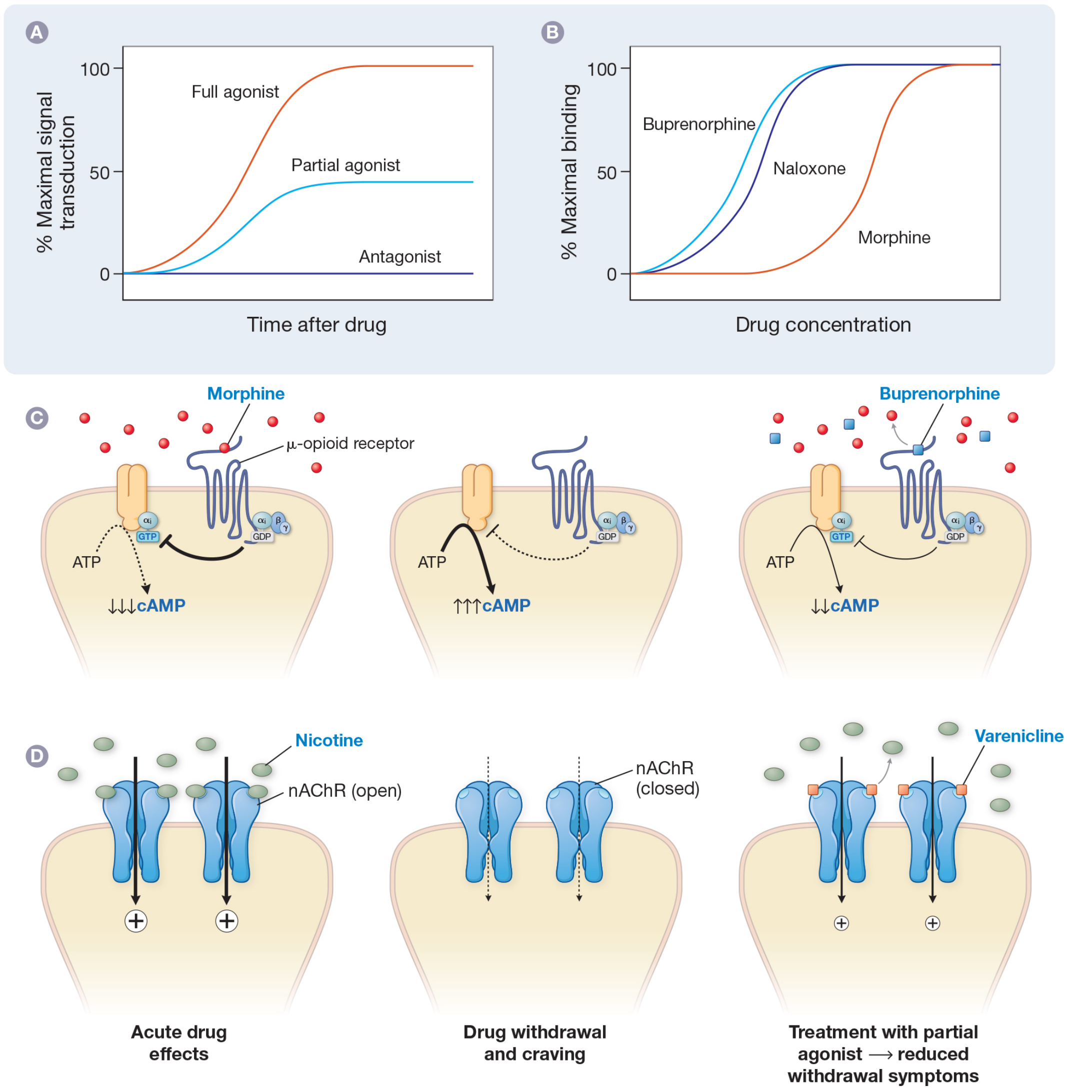


FIGURE 12-9 **Full and partial agonists.**
(Reprinted with permission from Golan DE, Armstrong EJ, Armstrong AW, et al. *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*. 4th ed. Wolters Kluwer; 2016. Figure 19-8.)

3. Bupropion
   a. Quit rates are similar to that of nicotine replacement therapy (twice that of placebo).
   b. The patient can take bupropion in combination with nicotine replacement therapy—combined use may result in higher quit rates than either method alone.

c. Adverse effects may include dry mouth, insomnia, and headaches. Contraindicated in patients with seizure disorder.

Health Maintenance

A. Screening for Hypertension

1. The United States Preventive Services Task Force (USPSTF) recommends screening all adults 18 years of age and older for HTN. However, other authorities do not recommend screening for HTN until middle age.

B. Screening for Hyperlipidemia

1. There is some debate about the optimal screening strategy. The USPSTF previously recommended in 2008 to screen all men ≥35 and women at risk for CAD ≥45 (grade A); the guidelines also recommend screening men aged 20 to 35 years at increased risk for CAD and women aged 20 to 45 years at increased risk for CAD (grade B). This recommendation is considered out of date, and the USPSTF has since made recommendations on statin use and not on the optimal lipid screening age and frequency.
2. Many providers will check a lipid panel when a patient establishes care. If normal and low cardiac risk, then they can have a repeat test at age 35 for males and 45 for females. If high cardiac risk, then a repeat test can be done at age 25 to 30 years in males and 30 to 35 in females.
3. Repeat testing can be performed every 3 to 5 years. Repeat testing is also recommended in patients on a statin to determine medication compliance and need for additional medications (e.g., ezetimibe, PCSK9 inhibitor).

Quick HIT

For average-risk patients, any of the following CRC screening tools can be used (see text for frequency): FOBT, FIT, stool DNA-FIT, CT colonography, flexible sigmoidoscopy, and colonoscopy.

C. Colorectal Cancer Screening/Surveillance (2021 USPSTF guidelines)

1. Screening is typically recommended starting at age 45 years for patients at average risk.
2. USPSTF recommendations: all patients should be screened at ages 50 to 75 years (grade A). Screening younger patients (45 to 49 years) or older patients (76 to 85 years) is a grade B and grade C recommendation, respectively
3. Screening options include:
   a. Colonoscopy every 10 years
   b. Flexible sigmoidoscopy every 5 years
   c. Flexible sigmoidoscopy every 10 years + annual fecal immunochemical test (FIT)
   d. CT colonography every 5 years
   e. Fecal occult blood test (FOBT) or FIT every year
4. Stool DNA-FIT every 1 to 3 years. High-risk patients typically begin screening at a younger age, depending on the diagnosis and family history of CRC. For example, patients with a family history (first-degree relative) of CRC should begin screening at age 40 years or at least 10 years before the age that the first-degree relative was diagnosed with CRC. Other examples of earlier screening and more frequent screening includes patients with IBP, familial adenomatous polyposis, history of advanced polyp on prior screen, etc.

D. Prostate Cancer Screening

1. This is controversial.
2. The USPSTF recommends men aged 55 to 69 years undergo periodic screening with prostate–specific antigen (PSA) on an individual basis (when the risks and benefits of screening and subsequent evaluation is discussed with the patient and they desire screening). This is a grade C recommendation. The USPSTF recommends against screening with PSA after the age of 69 years.

E. Lung Cancer Screening

1. The USPSTF recommends annual screening with low-dose CT in patients aged 50 to 80 years who have a 20 pack-year smoking history

and currently smoke, or quit within the last 15 years.

F. Women's Health

1. Breast cancer
   a. USPSTF—mammogram every 2 years for women 50 to 74 years of age
   b. Other groups recommend screening in women aged 40 to 49 years on an individual basis, and 75 years and older if the life expectancy is at least 10 years.
2. Cervical cancer
   a. The USPSTF recommends screening women aged 21 to 65 years.
   b. Women 21 to 29 years, screen with cervical cytology every 3 years.
   c. Women 30 to 65 years, screen with cervical cytology every 3 years, every 5 years with HPV testing, or every 5 years with HPB testing and cytology.
3. The USPSTF recommends against cervical cancer screening in women younger than 21 years, older than 65 years (who have had adequate prior screening without additional cervical cancer risk factors), and in women that have had a hysterectomy with the cervix removed.
4. Ovarian cancer
   a. Routine screening is not recommended

A 64-year-old woman presents to the physician with the request of being screened for bladder cancer. She feels well and has no complaints, but her sister just passed away from bladder cancer and she would like to determine if she has it as well. She smokes 2 packs of cigarettes per day and drinks 2 to 3 glasses of red wine per day. Physical examination shows an obese woman with wheezing on lung auscultation and an increased expiratory phase.

Which of the following is the most appropriate next step in management based on this patient's request?

A. Bladder tumor antigen testing
B. Urinalysis (UA)
C. Urinalysis (UA) and cytology
D. No screening

- **The answer is D: No screening.** Although bladder cancer is the second most common urologic cancer, the USPSTF states there is insufficient evidence to screen for bladder cancer. The recommendations are based on the fact that the current screening modalities (UA, cytology, bladder tumor antigen) all have a low positive predictive value in the general population. Therefore, screening for bladder cancer is not recommended even in those patients at risk for developing the disease (cigarette smoking, industrial chemical exposure, etc.).

G. Sexually Transmitted Infections

1. The USPSTF recommends screening for gonorrhea and chlamydia in women under the age of 24 years who are sexually active. Women 25 years and older should be screened if they are at an increased risk. The USPSTF says there is insufficient evidence to recommend this screening for men, whereas other groups will recommend it.
2. HIV screening in all patients aged 15 to 65 years (and beyond those years if risk factors are present). All pregnant patients should be

screened as well.

3. All patients at risk for syphilis should be screened. All pregnant patients should be screened.

H. Miscellaneous

1. Screening for diabetes mellitus:
   a. The USPSTF guidelines recommend screening for type 2 diabetes mellitus and prediabetes in adults aged 35 to 70 years who are overweight or obese.
   b. The American Diabetes Association recommends screening all adults with a BMI $\geq$25 kg/m^2 and at least one risk factor for diabetes every 3 years with hemoglobin A1c, fasting plasma glucose, or a 2-hour oral glucose tolerance test (OGTT). Adults without risk factors should be screened starting at the age of 45 years.
2. The USPSTF recommends screening for hepatitis B virus in patients at risk—injection drug use, men who have sex with men (MSM), hemodialysis, etc.
3. The USPSTF recommends screening for hepatitis C virus in all patients aged 18 to 79 years.
4. In elderly patients, assess risk factors for PAD, osteoporosis, stroke, and CAD.
5. Osteoporosis—DEXA scan starting at the age of 65 years in women (see Osteoporosis section for details).
6. AAA screening with a one-time ultrasound in men aged 65 to 75 years who have ever smoked.
7. The USPSTF recommends screening all adults for depression and alcohol misuse (and providing appropriate treatment and follow-up). The USPSTF does not recommend for or against screening for dementia.
8. Routine screening for thyroid disease is not recommended by the USPSTF, though some expert groups recommend it.

A 22-year-old woman presents for a routine annual physical examination. She has no complaints. She smokes 2 packs of cigarettes per day and drinks 2 glasses of wine per day. She is sexually active with one male partner and two female partners. She reports using oral contraceptive pills for birth control and consistent condom use with her male partner. Her family history is significant for breast cancer on her maternal side (aunt) and colon cancer on her paternal side (father died of colon cancer at the age of 52 years).

What is the recommended screening measure at this patient's visit?

A. Colonoscopy
B. *Chlamydia trachomatis* screening
C. Lipid panel
D. Mammogram

- **The answer is B: *Chlamydia trachomatis* screening.** The U.S. Preventive Services Task Force (USPSTF) recommends screening for Chlamydia in all sexually active women 24 and younger, and older women at increased risk.

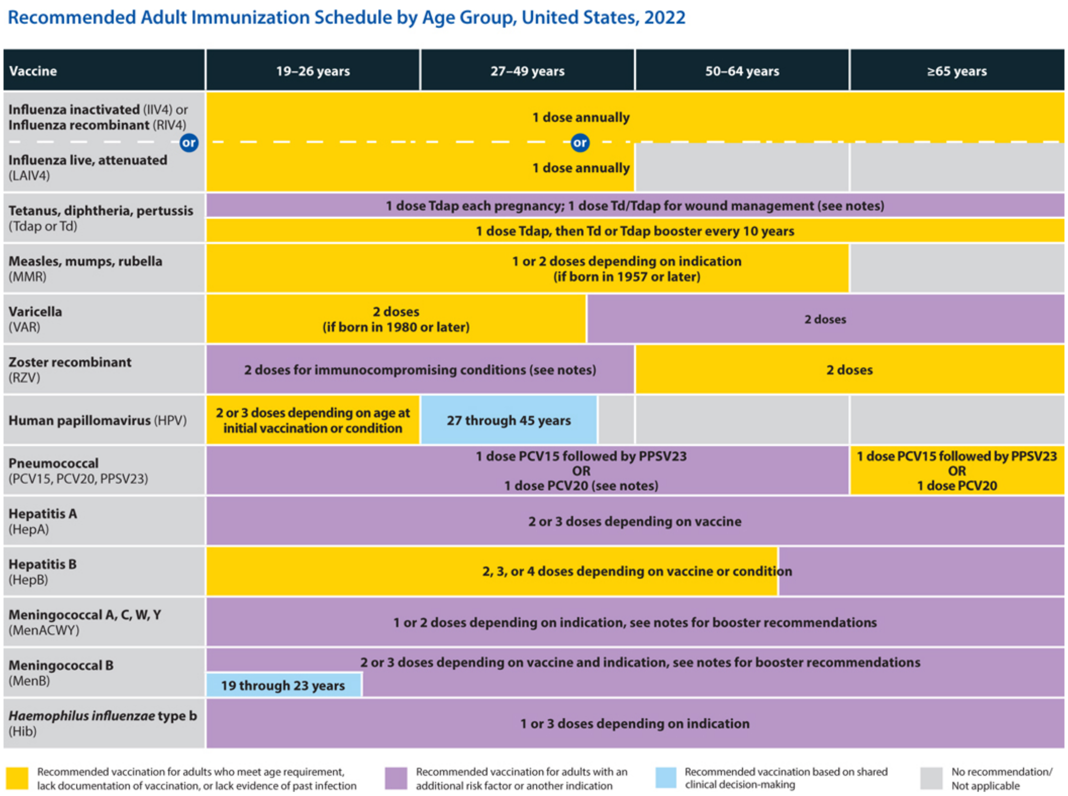


FIGURE 12-10 From https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html.

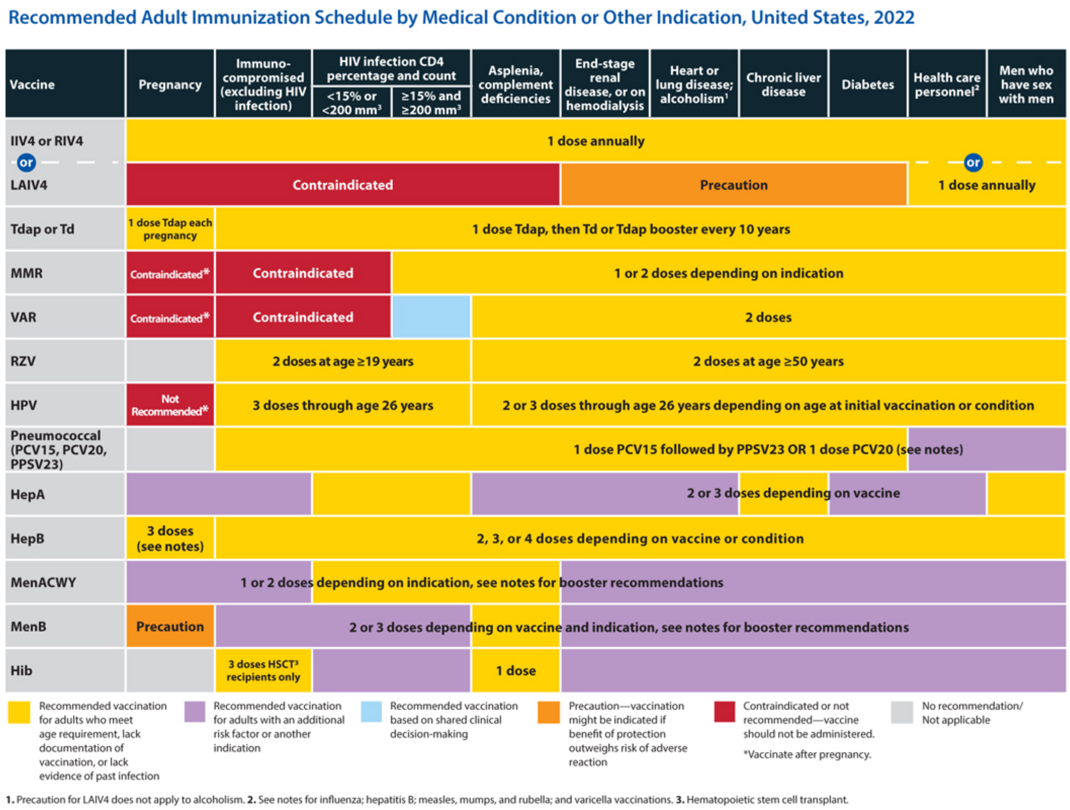


FIGURE 12-11 From https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html.

Quick HIT

Remember that functionally or anatomically asplenic individuals are at risk for infection with encapsulated organisms, so they should receive the *H. influenzae* type B (HIB) vaccine, meningococcal and pneumococcal vaccines.

I. Vaccinations

1. The most updated vaccination recommendations are based on the Advisory Committee on Immunization Practices (ACIP) and approved by the Centers for Disease Control and Prevention (CDC) and other groups.
2. See Figures 12-10 and 12-11. Further updates can be found at cdc.gov.

APPENDIX

Radiographic Interpretation

Chest Radiograph

A. Views: Obtain PA and lateral views for all patients who are well enough to be transported to the radiology department and maintain an upright position. Obtain an AP film (i.e., portable chest radiograph [CXR]) for all patients who are too ill to be transported and positioned for a PA film.

B. Always Try to Compare a Patient's CXR With a Previous Film to note any changes in condition and to assess whether changes are new or chronic.

C. Density: The lower the density, the more radiolucent (or transparent) the object will appear on plain radiographs. Following are structures in the body (main composition) listed from most radiolucent to most radiopaque: Air (lungs, trachea, gastric bubble), fat (breasts), fluid (most of the structures have high fluid content [e.g., vessels, heart, soft tissues]), bone, metallic foreign bodies (e.g., bullets, orthopedic hardware).

D. Assessment of the Film's Quality

1. Assess penetration
   a. The intervertebral spaces should be visible on a good-quality film.
   b. The outline of the vertebral bodies should be visible within (or through) the cardiac silhouette.
2. Assess inspiratory effort

a. A CXR is usually taken at the end of a full, deep inspiration. You should be able to see at least nine posterior ribs on the right side above the diaphragm. In general, if the diaphragm is crossing the tenth rib posteriorly (or the eighth rib anteriorly), inspiratory effort is optimal.
b. Patients who are ill or unable to follow directions may not be able to hold a full, deep breath for the CXR, leading to a poor inspiratory effort.
c. The heart appears larger than it actually is when there is poor inspiratory effort, which can be misleading.

3. Assess for rotation
   a. There should be symmetrical spacing of the clavicles on either side of the sternum, otherwise the patient is rotated.
   b. Imagine a horizontal line connecting the clavicular heads and a vertical line down the midline connecting the spinous processes of the vertebrae—these lines should be perpendicular to one another.

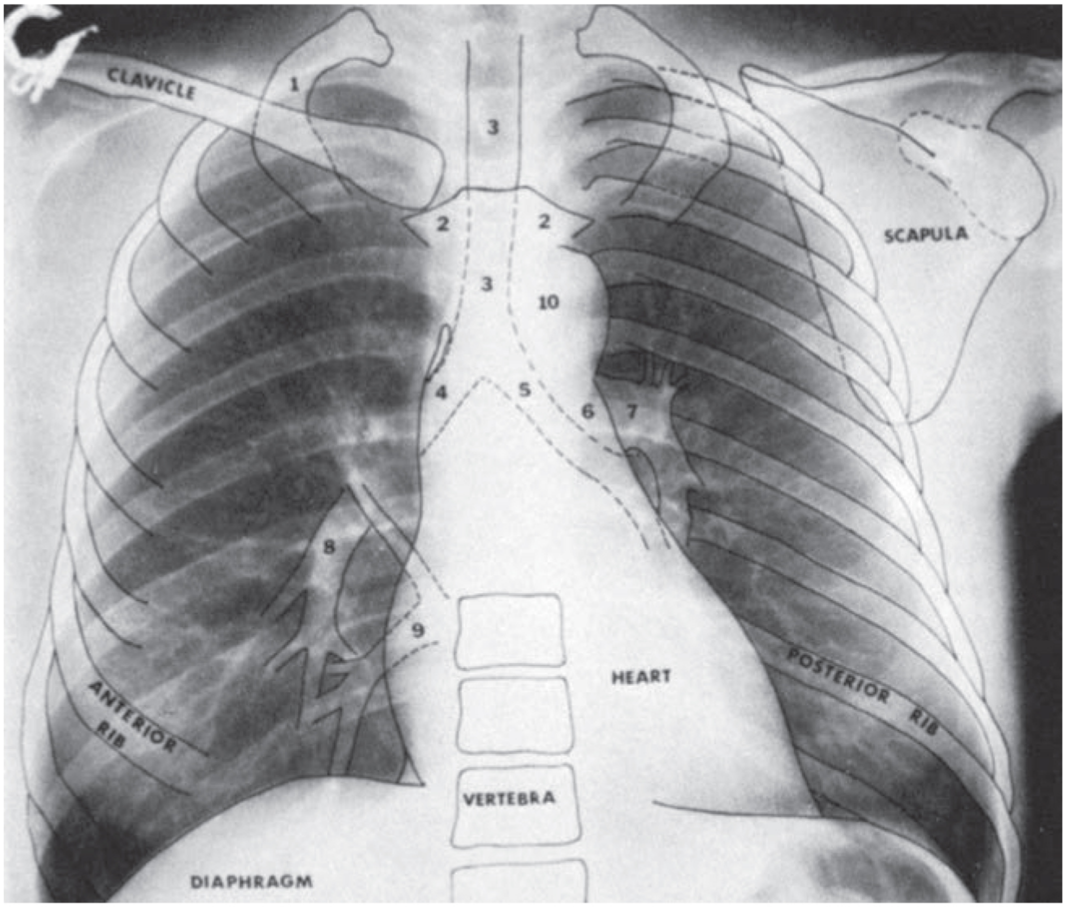
Quick HIT

Proper position of lines, tubes, and catheters

- Endotracheal tube—the tip should be approximately 4 to 6 cm above the tracheal carina (this is about the level of the clavicular heads) when the patient's head is neither flexed nor extended. The endotracheal tube tip can move up to 2 cm with extension or flexion of the head.
- Central line—the ideal placement of central line tip is unknown. The tip should be just above the right atrium in the superior vena cava. Placement in the right atrium also appears safe and may be specifically recommended for hemodialysis catheters. Previously, it was thought that placement in the right atrium would lead to higher risk of cardiac perforation or arrhythmia (but this does not seem to be the case in studies).
- Swan–Ganz catheter—the tip should be within the proximal right or left main pulmonary arteries within the mediastinal shadow. If more distal to this there is higher chance of pulmonary infarction or vessel rupture.
- Nasogastric tube—the tip should be distal to the esophagogastric junction in the stomach. A good rule of thumb is to ensure the nasogastric tube tip is below the diaphragm and does not traverse the course of the carina into the lung.

E. Examination of the PA/AP CXR (Figure A-1): No one approach is standard.

1. "ABCDE" approach:
   a. Airway
   b. Breathing (lung parenchyma and pleural spaces)
   c. Circulation (cardiac size, cardiac borders)
   d. Diaphragm (hemidiaphragm levels, cardiophrenic and costophrenic angles)
   e. E: everything else (bones, gastric bubble, devices)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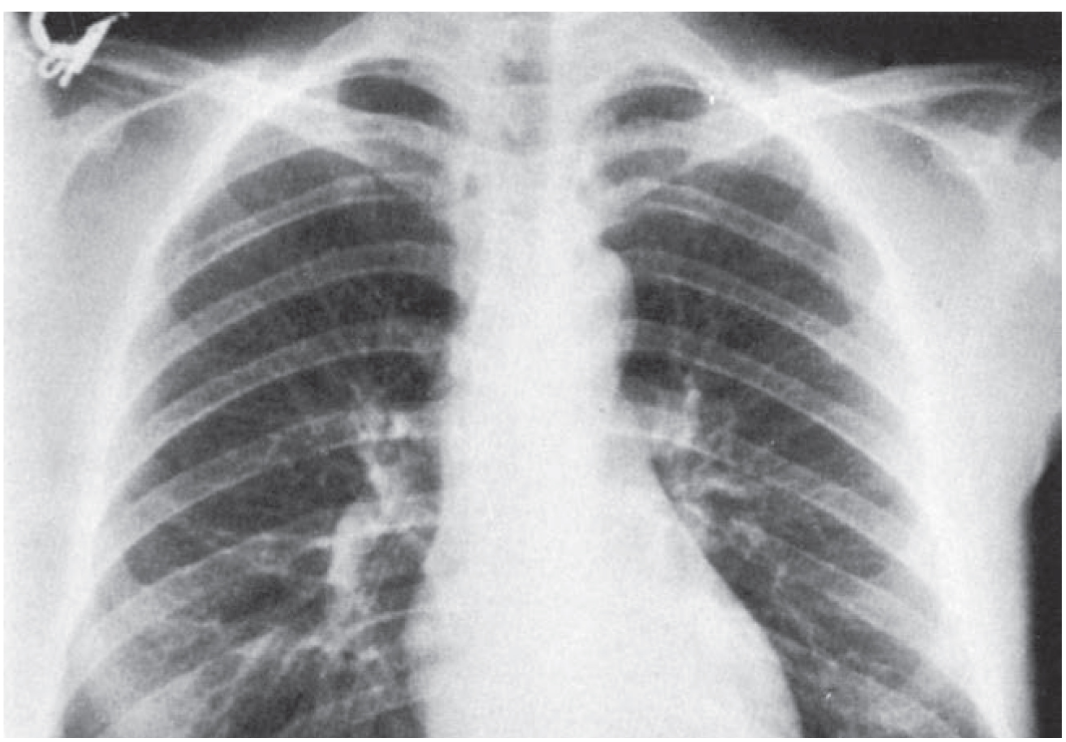

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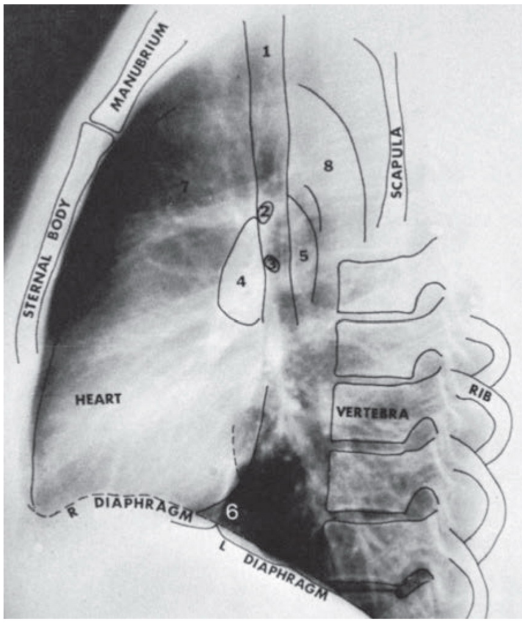

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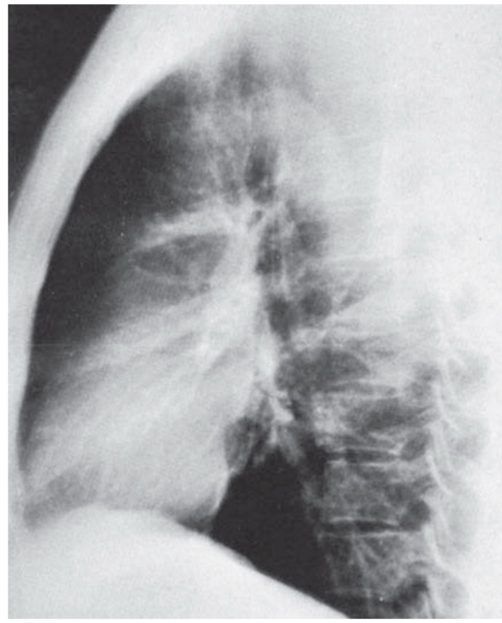

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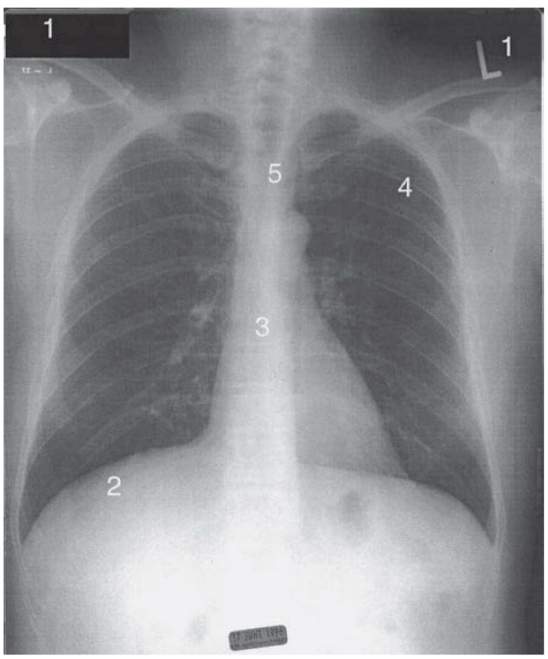


E

FIGURE A-1 **A: PA CXR with diagrammatic overlay: *1,* first rib; *2,* upper portion of manubrium; *3,* trachea; *4,* right main bronchus; *5,* left main bronchus; *6,* main pulmonary artery; *7,* left pulmonary artery; *8,* right interlobar pulmonary artery; *9,* right pulmonary vein; *10,* aortic arch. B: CXR of the same subject without diagrammatic overlay.**

(**A** and **B** reprinted with permission from George RB, Light RW, Matthay MA, et al. *Chest Medicine: Essentials of Pulmonary and*

Critical Care Medicine. 4th ed. Lippincott Williams & Wilkins; 2000:69. Figure 5.1A and B.)

C: Lateral CXR of the same patient as in A: *1,* trachea; *2,* right upper lobe bronchus; *3,* left upper lobe bronchus; *4,* right pulmonary artery; *5,* left pulmonary artery; *6,* inferior vena cava; *7,* ascending aorta; *8,* descending aorta. D: Same lateral CXR without diagrammatic overlay. E: Technical adequacy of a CXR: *1,* a technically adequate CXR should be labeled with the patient's name, date, and a side marker; *2,* the midportion of the right hemidiaphragm should be below the 10th rib; *3,* vertebral bodies should be visualized throughout the spine; *4,* pulmonary vessels should be visible to the outer third of the lung; *5,* the thoracic spinous processes should be midway between the heads of the clavicle.

(**C** and **D** reprinted with permission from George RB, Light RW, Matthay MA, et al. *Chest Medicine: Essentials of Pulmonary and Critical Care Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:70. Figure 5.2A and B. **E** reprinted with permission from Humes HD, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Lippincott Williams & Wilkins; 2000:2570. Figure 386.3.)

2. Whichever approach you use, make sure to observe the following points:
   a. Examine bones: shoulders, clavicles, cervical and thoracic spine, and ribs—on PA films, the horizontal ribs are posterior (anterior ribs are angled downward).
   b. Evaluate cardiac size: the transverse diameter of the cardiac silhouette should not be more than half the transverse diameter of the thorax; this is the cardiothoracic ratio. (A larger cardiothoracic ratio is acceptable for an AP film because the cardiac silhouette is larger on an AP film.)
   c. Check for mediastinal widening, which may be present in aortic dissection, trauma, and mediastinal masses such as lymphoma.
   d. Evaluate the position of the trachea; it should be in the midline.
   e. Compare right and left lung fields. It is best to divide the lung fields into thirds (horizontally) and compare the two sides.
   f. Look for any infiltrates or consolidation.
   g. Congestion—look for enlarged cardiac silhouette, pulmonary vessels that are more visible and extend further into the lung field than normal ("cephalization" of the pulmonary vessels).

h. Pneumothorax—look for a line demarcating free air (hyperlucent with no pulmonary vascular markings) in the pleural space.
i. Pleural effusion—examine the costophrenic angles; they should be sharp and clear without any blunting.
j. Look at the diaphragms—the right diaphragm is normally slightly higher than the left due to presence of the liver.

F. Examination of the Lateral Film (see Figure A-1).

1. Look at the cardiac silhouette
   a. Anterior border—formed by the right ventricle
   b. Posteroinferior border—formed by the left ventricle
   c. Posterosuperior border—formed by the left atrium
   d. The right atrium cannot be seen
2. Look at the trachea
3. Examine the retrosternal and retrocardiac spaces for any abnormalities
4. Examine the diaphragms—note that the anterior portion of the left hemidiaphragm is not visible because of the cardiac silhouette. The entire right hemidiaphragm should be visible, however

Abdominal Radiographs

A. The Standard Abdominal Film —KUB—is a supine view, which is ideal for seeing the gas pattern.

B. Order an Obstruction Series (includes PA CXR, as well as supine and upright abdominal films) to evaluate the gas pattern and to look for the following:

1. Free intraperitoneal air (see later)—free air is seen under the diaphragm on the CXR. If the patient is too ill to be upright, order a left lateral decubitus film instead (air rises to the nondependent area).
2. Air–fluid levels—seen on the upright film (see later).

C. Most Important Things to Look for on Abdominal Films

1. Air–fluid levels—sign of obstruction; if prominent and multiple, mechanical obstruction is more likely than ileus.
2. Free air under the diaphragm (perforation of a viscous)—this is a surgical emergency.
3. Dilated loops of bowel (obstruction, ileus)—it may be difficult to distinguish mechanical obstruction from ileus. The following may help:
   a. If air is in the small intestine, colon, and rectum, ileus is more likely because ileus distention involves the entire GI tract.
   b. In small bowel obstruction, there are distended loops of small bowel proximal to the site of obstruction and multiple air–fluid levels on upright or decubitus films. Colonic gas is usually minimal.
   c. In large bowel obstruction, look for haustral markings—they span one-half to two-thirds of the diameter of large bowel—as well as the colonic shadow on the periphery or in the pelvis.
   d. In an ileus, the dilated loops are scattered and lack organization (e.g., like a "bag of popcorn"); in mechanical obstruction, dilated loops are stacked on top of one another (e.g., like a "bag of sausages").
   e. Too little gas in the abdomen can be due to high obstruction.

Electrocardiogram Interpretation

Electrocardiogram Pearls

A. Always Look for an Old Electrocardiogram (ECG) With Which to Compare the Current ECG.

This is critical in assessing whether any significant changes have occurred.

B. Determine Rate

1. Count the number of large blocks (with five little squares) between each R wave. Divide this number by 300 (the distance between large

blocks represents 1/300 minute). Therefore, if there are four blocks between each R wave, there is 4/300 or 1/75 minute between each R wave, which means that the rate is 75. (Note that this is the same as the 300-150-75-60-50 rule.)

2. If the rate is irregular, count the number of beats in 6 seconds and multiply by 10.
3. Each block is 1 mm (0.04 seconds), so five boxes equal 0.20 seconds (or 200 ms).
4. Tachycardia is defined as a rate >100 beats/min.
5. Bradycardia is defined as a rate of <60 beats/min.

C. Determine Rhythm (look at lead II)—is the rhythm regular or irregular? Note that rhythms may be regularly irregular or irregularly irregular as well. (See Chapter 1, Arrhythmias section.)

1. Is the rhythm originating from the sinus node?
   a. Is there a P wave preceding each QRS?
   b. Is there a QRS after each P wave?
   c. Is the P wave upright in lead II?
   d. If the answer to all of the above is yes, this is likely sinus rhythm.

D. Determine Axis

1. Look at the QRS complex in leads I and aVF.
2. If both are mainly positive, then the axis is normal.
3. If mainly positive in lead I and mainly negative in aVF, the axis is deviated to the left.
4. If mainly negative in lead I and mainly positive in aVF, the axis is deviated to the right.
5. If mainly negative in both I and aVF, then there is extreme right axis deviation.
6. If lead aVF is isoelectric (meaning it is neither positive nor negative), look at lead II as the "tie breaker" since lead II is also an inferior lead. The same rules apply for lead II as for lead aVF.

E. Intervals

1. P-R interval—this should be between 120 and 200 ms (three to five small boxes).

a. In **first-degree heart block**, the P-R interval is >200 ms (one large box).
b. In **second-degree AV block** (Wenckebach or **Mobitz type I**), there is a progressive lengthening of the P-R interval followed by a dropped QRS complex.
c. In the **Mobitz type II** form of second-degree heart block, the P-R interval is constant, but not every P wave is followed by a QRS complex. There may be two, three, or even more P waves before a QRS, but the ratio of P waves to QRS complexes (e.g., 2:1, 3:1) is constant.
d. In **third-degree heart** block, there is no relationship between atrial (P waves) and ventricular (QRS) activity.
e. A short PR interval (<120 ms) suggests the presence of a pre-excitation pathway (an accessory pathway between the atria and ventricles) or a junctional rhythm (originating from the AV node).

2. QRS complex—this should be <120 ms.
a. Prolongation of the QRS complex is seen in bundle branch block, other conduction blocks, ventricular rhythms, and paced rhythms.
b. In **right bundle branch block (RBBB)**, look for a widened QRS complex, an rSR wave in the chest leads, and a wide S wave in lead I.
c. In **left bundle branch block (LBBB)**, look for a widened QRS complex and loss of Q waves with broad, notched R waves in leads I, V_5, or V_6.

3. QT interval—the normal QT interval should be less than half of the R-R interval (<440 ms in men, <460 ms in women). Prolongation of the QT interval may be seen in the following.
a. Medications: too many to list. Common examples: tricyclic antidepressants, fluoroquinolones, antipsychotics, antihistamines, some antiemetics; class IA, IC, and III antiarrhythmics.
b. Electrolyte disturbances: hypocalcemia, hypokalemia, hypomagnesemia.
c. Congenital long QT syndromes.
d. Other: ischemia, significant bradyarrhythmias, and increased intracranial pressure.

F. Examine Waves

1. P waves—there should be one P wave for each QRS complex in a normal sinus rhythm. The P wave should be upright in lead II (indicating that it is originating in SA node with atrial depolarization toward lead II)
   a. **Left atrial enlargement**—wide P wave (>120 ms) in lead II or a diphasic P wave with a deep terminal component in V_1
   b. **Right atrial enlargement**—tall P wave (>2.5 mm) in lead II or a diphasic P wave with a large initial component in V_1
   c. **Wandering atrial pacemaker (if HR <100)**—at least three different P-wave morphologies are present. This is also called multifocal atrial tachycardia if HR >100
2. Q waves—indicate myocardial necrosis (acute or old MI)
   a. To be considered significant, they must be more than 1 small box wide (0.04s) and >25% of the QRS amplitude
   b. Isolated Q waves in certain leads may be normal, especially in aVR
3. QRS complex
   a. Should be narrow (<120 ms) with a regular morphology
   b. The following are indicators of left ventricular hypertrophy (LVH). There are multiple criteria for diagnosing LVH (not all listed here), but only one needs to be met for a diagnosis of LVH
      - R wave in V_5 or V_6 >26 mm high
      - S wave in V_1 + R wave in V_5 or V_6 >35 mm high in adults (>age 30 years)
      - R wave in aVL ≥11 mm
      - Left-axis deviation is often present (this does not need to be met for LVH to be present).
   c. The following are indicators of right ventricular hypertrophy (RVH) (assuming QRS duration <120 ms, since RBBB can produce these changes as well)
      - R wave ≥7 mm in V_1
      - R/S ratio in V_1 ≥1
      - Progressive decrease in R-wave height across the precordial leads
      - Right-axis deviation is often present

Quick HIT

Large R waves and ST segment depressions in V_1 or V_2 suggest a posterior wall MI.

4. ST segments
   a. Always compare the ST segment to the baseline of the T-P interval (between the T wave to the next P wave; do not compare ST segments against the PR segment, as this can be altered in disease states)
   b. ST segment depression can occur in the following conditions:
      - Myocardial ischemia
      - Subendocardial MI
      - Digoxin effect
      - Hypokalemia
      - LBBB or RBBB
      - LVH with abnormal repolarization
   c. ST segment elevation is a key indicator of myocardial necrosis—it is a hallmark of acute transmural MI, but may persist in an old MI
      - ST segment elevations in I, aVL, V_5, and V_6 are consistent with a lateral wall MI (left circumflex coronary artery)
      - ST segment elevations in V_1 to V_4 are consistent with an anteroseptal wall MI (left anterior descending coronary artery)
      - ST segment elevations in II, III, and aVF are consistent with an inferior wall MI (terminal branches of right or left coronary artery)
      - Diffuse ST segment elevations may be present in pericarditis
      - Small, concave ST segment elevations may be a normal finding in young people (early repolarization)
      - If LBBB is present, ST segment elevations may be present and are an unreliable indicator of ischemia/infarction
5. T waves
   a. Peaked T waves may be present in the following situations:
      - Very early stages of MI (before true infarction occurs)
      - Hyperkalemia
      - Hypermagnesemia
   b. T-wave inversions may be present in the following situations:

- Myocardial ischemia/infarction
- Pericarditis
- Cardiomyopathy
- Intracranial bleeding
- Electrolyte disturbances, acidosis
- LBBB, LVH
- Small T-wave inversions may be normal in the limb leads

Intravenous Therapy

A. Forms of IV Therapy

1. "Intravenous (IV) push"—this is administration of a medication directly into the IV access. It is typically used in emergency situations when a rapid response is needed or when a loading dose of a medication is to be given, followed by a continuous infusion.
2. Continuous administration—electronic devices deliver fluid or medication at a preset volume per hour.
3. Intermittent administration can be accomplished via a number of methods.
   a. Heparin lock or saline lock—this is used when the patient no longer needs IV fluids and IV medications can be given intermittently. The IV line is kept open with saline or heparin when no medication is being given.
   b. Piggyback—a medication or solution is given through another established primary infusion. The first bag that is hung is the primary infusion. Tubes from both the primary bag and the piggyback bag connect to a common tube that feeds into the patient's vein.
   c. Nontunneled central catheter—the exit site of the catheter is at the skin. Locations include internal jugular (IJ), femoral, and subclavian veins.
   d. Tunneled central catheters (e.g., Hickman)—the catheter is inserted into the subclavian vein, but the end of the catheter is then "tunneled" in the subcutaneous tissue so that it exits the skin away from the site of vein insertion. With both nontunneled and tunneled central catheters, there is easy access but also the risk of infection at

the exit site (although infection risk is lower with a tunneled central catheter).

e. Ports—the catheter is inserted into a central vein and is tunneled subcutaneously. There is not an exit site because the catheter attaches to the port (chamber) that is placed subcutaneously as well. To administer medication, an anesthetic agent is used to numb the skin, and the needle is inserted into the chamber. Often used for chemotherapy administration. Port-a-Cath is an example. There is less risk of infection (no exit site), but access is more difficult and must be performed by a trained medical professional.
f. Peripherally inserted central catheter (PICC) line—these are often used to administer IV antibiotics at home (or blood products, other medications, or chemotherapy). Locations include cephalic, basilic, or brachial veins. A PICC is inserted through the veins of the antecubital fossa, and the tip is advanced into the super vena cava. It can be left in place for weeks to months.

B. Complications of IV Therapy

1. Thrombophlebitis—manifested by redness, swelling, and pain at IV site; can be prevented by changing the IV every 2 to 3 days. Treat by removing the IV and applying warm compresses
2. Infiltration—medication/fluid leaks into the surrounding tissue. This is usually benign, unless the medication that extravasated into surrounding tissue causes significant tissue damage (e.g., vasopressors). If it is significant and involves a large area, it may lead to compartment syndrome
3. Blockage
4. Air embolus

Quick HIT

- Immediately after placing a central line (IJ or subclavian), obtain a CXR to check for pneumothorax and to ensure proper position of the catheter tip. The catheter tip should be in the superior vena cava just above the right atrium. Placement in the right atrium is also safe (and in some cases may be preferred, especially for hemodialysis catheters).
- When removing a line, the patient should be in Trendelenburg position and should exhale or hum during removal to prevent an air embolism.

Central Venous Line

A. Indications

1. Hemodynamic monitoring (e.g., placement of a pulmonary artery catheter, although this is not often done)
2. Transvenous pacing
3. Emergent or short-term hemodialysis
4. Emergent delivery of IV medications (particularly in cardiac arrest)—if feasible, it is generally preferable to have a central venous catheter over a peripheral catheter for the administration of drugs in cardiac arrest because the medication is delivered to the heart and the arterial vasculature more rapidly
5. To administer total parenteral nutrition (TPN)—the high concentration makes it difficult to administer this through peripheral veins
6. Administration of medications that can be harmful if given peripherally
   a. Irritating medications, which can cause thrombophlebitis or tissue damage in peripheral veins (e.g., high-concentration potassium chloride, chemotherapy)
   b. Vasopressors—cause arterial vasoconstriction and should not be given through peripheral lines for extended periods of time, because if infiltration occurs in a peripheral line, it may cause compartment syndrome or soft tissue necrosis
7. Volume replacement (fluid or blood)—if large volumes of fluid must be given rapidly, large-diameter central catheters (e.g., a sheath introducer such as a Cordis) are needed, particularly if the patient does not have adequate peripheral access. (But in general, peripheral IVs

are ideal for rapid fluid resuscitation since the flow rate of fluids is inversely proportional to the length of the catheter.)

8. Although routine or frequent blood draws are not an indication for central venous line placement, an already-existing central line can be used for this purpose

Quick HIT

Pulmonary Artery Line

- A central catheter that is inserted through one of the large veins, threaded through the right ventricle, and into the pulmonary artery.
- Also known as a "Swan–Ganz catheter."
- Used to measure various hemodynamic parameters, including central venous pressure, pulmonary capillary wedge pressure (PCWP), cardiac index and output, stroke volume, and systemic vascular resistance.

B. Sites

1. IJ vein
2. Subclavian vein
3. Femoral vein

C. Complications

1. Pneumothorax
   a. Can occur with subclavian lines and IJ lines (but more common with subclavian lines); does not occur with femoral lines
   b. Note that patients with elevated PEEP have hyperinflated lungs, and the apex of the lungs is more superior than normal, increasing the chances of an iatrogenic pneumothorax
2. Venous air embolism—if air is sucked into the vena cava, it can be pumped through the right ventricle into the lungs, leading to pulmonary embolism (PE) of air. This is a potentially life-threatening complication. If the patient has a patent foramen ovale, it can result in a paradoxical air embolism to the brain
3. Puncture of adjacent artery (carotid, subclavian, or femoral)—depending on the site, this can lead to complications including hemothorax (subclavian) and hematoma (IJ and femoral). Apply

compression if this occurs. Emergent vascular surgery consultation is needed

4. Infection—central lines can cause central line–associated blood stream infections, which can be life-threatening
5. Deep vein thrombosis and thrombophlebitis
6. Cardiac arrhythmias—this can occur during insertion if the guidewire is too deep and irritates the myocardium. Patient should always be on cardiac monitor during central line insertion

Quick HIT

There are two means of providing nutrition for a patient who cannot eat: enteral nutrition and parenteral nutrition.

Arterial Lines

- Definition—IV catheters (same ones used for peripheral lines) that are inserted into the radial artery (rarely in ulnar or brachial artery).
- Uses—arterial lines have two major uses.
  - Continuous BP monitoring is the most important—arterial lines give more accurate and instantaneous readings than noninvasive blood pressure cuffs. A patient on vasopressors generally should have an A-line for proper BP monitoring.
  - Used for frequent blood gas draws.

Quick HIT

- Percutaneous endoscopic gastrostomy (PEG) tube—the tube is inserted with the help of an endoscope through the mouth. Alternatively, it can also be inserted percutaneously by interventional radiology, or through an open abdominal incision by general surgery, which is called open gastrostomy. In this case, it is called a gastrostomy tube (G-tube).
- The J-tube (jejunostomy) is placed in the intestine and is inserted through an open abdominal procedure or through enteroscopy (a longer endoscope is needed).

Nutritional Support

A. Enteral Nutrition (administered into the GI tract)

1. Enteral nutrition is preferred over parenteral nutrition because the intestine is used in a physiologic manner.
2. There are two methods of administering enteral nutrition.
   a. Nasoenteric tubes (e.g., nasogastric or nasojejunal tubes)—best for short-term nutrition.
   b. Enterostomy tubes (e.g., PEG/G-tubes, J-tubes)—for long-term support.
3. There are many different formulas available for tube feeds—special formulas can be provided for patients with renal disease, liver disease, diabetes mellitus, and so on.
4. Tube feeds can be delivered intermittently (in boluses) or continuously.
   a. Bolus (intermittent) feeding (into the stomach) requires close nurse monitoring at initiation. There is no clear consensus on an appropriate cutoff level for a safe gastric residual volume. There is also no clear evidence that an elevated gastric residual volume is associated with adverse clinical outcomes such as mortality, pneumonia, or hospital length of stay. In general, most nursing protocols require monitoring gastric residual volumes every 6 to 8 hours. A high residual volume (usually considered to be >500 mL) in a patient with elevated aspiration risk may prompt holding of tube feeds temporarily. However, this does not always necessitate stopping tube feeds.
   b. Contrary to popular belief, the risk of aspiration pneumonia does not differ between continuous pump feeding and intermittent bolus feeding.
   c. Postpyloric (duodenal or jejunal) feeding may decrease risk of aspiration pneumonia in high-risk patients, when compared to gastric feeding. There is limited evidence that one method is superior to another in terms of clinical outcomes such as mortality, length of stay, or duration of mechanical ventilation.
5. Complications of enteral nutrition.
   a. Intolerance to tube feeds—check for diarrhea, constipation, nausea, vomiting, abdominal pain, or distention. If this occurs, discuss with

dietician and trial changing tube feed formulation.

b. Malpositioning of tube (in trachea/bronchus).

c. Aspiration pneumonia (the risk of aspiration is not lessened by enteral feeding compared to oral feeding).

d. Overload of solutes—due to high rate of hyperosmolar feedings (can cause diarrhea, electrolyte imbalance, hyperglycemia).

B. Parenteral Nutrition (administered into the vein)

1. The term TPN (total parenteral nutrition) is used for a high-concentration solution that can be given alone to meet the body's caloric demands. TPN can also play a supplementary role when enteral feeding alone is inadequate
2. It is used if the patient cannot eat for prolonged periods or cannot tolerate enteral feedings, and in severely malnourished patients
3. There are two formulations and methods of administration
   a. Central—TPN administered via central venous catheter (e.g., subclavian vein)—preferred in patients who require long-term support
   b. Peripheral—PPN (peripheral parenteral nutrition) is administered via peripheral line—one cannot administer as much protein or calories with this as with a central line. It should only be used for a short-term period. TPN cannot be administered via peripheral line as its high osmotic load is not well tolerated by peripheral veins.
4. Complications of parenteral nutrition
   a. Electrolyte imbalances, volume disturbances
   b. Hyperglycemia
   c. Complications associated with placing a central line (e.g., pneumothorax)
   d. Infection of central (or peripheral) line (higher rates of infection, especially with fungal organisms, than usual due to presence of nutrients and glucose)

Quick HIT

Best antibiotics for gram-positive cocci (Staph and Strep):

1. PRPs (oxacillin, nafcillin, etc.)
2. First-generation cephalosporins
3. Tetracyclines

Quick HIT

Hypersensitivity Reactions to Penicillin

- Type I hypersensitivity reaction.
- This may present with rash, angioedema, or even anaphylaxis.
- Cross-reactions with other β-*lactam* antibiotics can occur.
- Nausea, vomiting, and diarrhea are not hypersensitivity reactions.
- It may develop at any time, even if past treatments with penicillin were uneventful.

Guide to Antibacterial Antibiotic Therapy

A. Cell Wall Inhibitors

1. Penicillins (see Table A-1)
   a. Mechanism of action
      - A β-lactam antibiotic
      - Inhibit cross-linkage (transpeptidation step) of bacterial cell walls as they are synthesized
      - Bacterial cell walls lose structural and osmotic integrity
      - Cell lysis ultimately occurs
      - To achieve the desired effect, penicillins must first bind to proteins located inside the bacterial cell wall. These proteins are called penicillin-binding proteins
   b. Antimicrobial coverage (not exhaustive)
      - More effective against **gram-positive** than gram-negative organisms. Effective against viridans group streptococci, *Streptococcus pyogenes*, oral anaerobes, syphilis, Leptospira
      - Acts synergistically with aminoglycosides

- Penicillin G is a long-acting intramuscular form of penicillin which is the drug of choice to treat syphilis. Because of microbial resistance, it is used less commonly to treat respiratory tract infections caused by streptococcal species, such as pharyngitis secondary to *S. pyogenes* or pneumococcal pneumonia
- Penicillin V is the oral form of penicillin G which has some anaerobic activity, so it is more useful for dental infections
- Penicillins are not good choices for empiric coverage for most infections due to widespread resistance
- Ampicillin and amoxicillin have extended gram-negative activity. Ampicillin is typically given IV, while amoxicillin is an oral drug often used to treat outpatient upper respiratory tract infections caused by streptococcus. They cover the same organisms as penicillin, in addition to *Escherichia coli,* Lyme disease and few other gram-negative rods (*Haemophilus influenzae, Listeria, E. coli, Proteus, Salmonella*)
- Penicillinase-resistant penicillins (PRPs) include oxacillin, cloxacillin, dicloxacillin, and nafcillin
- Penicillins are generally ineffective against intracellular bacteria

c. Adverse reactions
- **Hypersensitivity reactions**—type I hypersensitivity reaction may present as rash, angioedema, or even anaphylaxis
- Diarrhea
- Acute interstitial nephritis

d. Other features
- Penicillins are used to treat otitis media, cystitis in pregnant women, dental infections, enterococcal infections, Listeria monocytogenes, Lyme disease
- Penicillin is used as prophylaxis against infection in patients with sickle cell disease
- Bacteria gain resistance to penicillins through alterations in penicillin-binding proteins—for example, MRSA
- Resistance is also conferred by β-lactamases, enzymes that hydrolyze the penicillin’s β-lactam ring. This can be overcome with the addition of a β-lactamase inhibitor, for example, ampicillin-sulbactam or amoxicillin-clavulanate

e. Examples (list of examples is not exhaustive)

- Penicillin G
- Penicillin V
- Ampicillin
- Amoxicillin
- Methicillin
- Nafcillin
- Oxacillin
- Dicloxacillin
- Piperacillin

TABLE A-1 Important Antibiotics

Antibiotic/Antibiotic Category	Mechanism of Action	Most Common Uses	Adverse Reactions Commonly Seen[a]
Penicillins	Cell wall inhibitors (interfere with transpeptidation)	Depends on extension of antimicrobial spectrum Oral and respiratory infections Streptococcal infections Syphilis	Hypersensitivity reactions
Vancomycin	Cell wall inhibitor (see text)	MRSA Enterococcal infections Endocarditis (used with aminoglycoside)	Nephrotoxicity, Vancomycin infusion syndrome
Tetracyclines	Inhibit 30 S bacterial ribosomal subunit	Chlamydia Rickettsiae Lyme disease Topical use for acne vulgaris	Deposition in bones and teeth of children >8 yrs old, fetuses
Macrolides	Inhibit 50 S bacterial ribosomal subunit	Atypical pneumonia Alternative to penicillin (i.e., allergy)	GI upset
Clindamycin	Inhibits 50 S bacterial ribosomal subunit	Anaerobes, staphylococci, streptococci	*C. difficile* colitis
Cephalosporins	Cell wall inhibitors (similar to penicillins)	Depends on generation: First: Similar to penicillins, surgical prophylaxis, streptococci and staphylococci infections Second: Pneumonia, intra-abdominal infections	Hypersensitivity reactions Encephalopathy and seizure *C. difficile* colitis

		Third: Pneumonia, intra-abdominal infections, gonorrhea, meningitis Fourth: Broad-spectrum, including streptococci, staphylococci, and pseudomonas Fifth: MRSA infections	
Carbapenems	Cell wall inhibitors (more resistant to β-lactamases and penicillinases)	Penicillin-resistant pneumococci, *Pseudomonas* (except ertapenem), anaerobic infections	Encephalopathy and seizure
Fluoroquinolones	Inhibit bacterial DNA gyrase	UTIs Diarrhea secondary to gram-negative rods Penicillin-resistant pneumonia Some with anti-Pseudomonas activity	Many Damage to cartilage in children Tendon rupture QT prolongation
Aminoglycosides	Inhibit 30 S bacterial ribosomal subunit	Gram-negative sepsis Endocarditis (with vancomycin) Complicated UTIs	Nephrotoxicity Ototoxicity
TMP/SMX	Blocks bacterial DNA synthesis through action on folate pathway (two steps)	*P. carinii* pneumonia UTIs	Rash Stevens–Johnson syndrome AIN, hyperkalemia
Metronidazole	Products of reduction reaction kill susceptible bacteria and protozoans	Anaerobes *Trichomonas histolytica* and *Giardia*	Metallic taste Peripheral neuropathy

[a]Note that these are not necessarily the most common side effects.

Quick HIT

Best antibiotics for anaerobes:
1. β-Lactam plus β-lactamase inhibitor
2. Clindamycin
3. Metronidazole (for abdominal/GI)
4. Carbapenems

Quick HIT

All cephalosporins (every generation) will cover viridans group streptococci, group A, B, and C streptococci, *E. coli, Klebsiella, Proteus mirabilis.*

Quick HIT

First-generation cephalosporins are mostly active against gram-positives. With each ascending generation, there is more activity against gram-negative strains (and less activity against gram-positives, except for fourth-generation cephalosporins which have broad activity).

2. **Cephalosporins**
   a. Mechanism of action
      - Similar mechanism of action to penicillin
      - As with penicillin, the β-lactam ring confers **bactericidal** activity
   b. Antimicrobial coverage (not necessarily exhaustive—this applies to the rest of antimicrobial section)
      - Cephalosporins are classified according to antimicrobial activity and β-lactamase resistance into "generations"
      - First-generation cephalosporins generally serve as substitutes for penicillin, and also have coverage against *Proteus, Klebsiella,* and *E. coli.* Cefazolin is the only parenteral first-generation cephalosporin available in the United States
      - Second-generation cephalosporins have more gram-negative activity and less gram-positive activity than first-generation cephalosporins. They are used to treat *H. influenzae, Neisseria gonorrhoeae,* and *Enterobacter* spp.

- Third-generation cephalosporins have even more **gram-negative activity, less gram-positive activity,** and are **able to cross the blood–brain barrier. (First- and second-generation cephalosporins do not penetrate the CSF and should not be used to treat infections of the central nervous system)**
- Fourth-generation cephalosporins are the most broad-spectrum, including activity against *Pseudomonas, Neisseria,* and methicillin-sensitive *Staphylococcus aureus*, as well as most of the above-mentioned organisms. They have better staphylococcal coverage than third-generation drugs
- Fifth-generation cephalosporins are a new class of drugs which show high activity against MRSA and other multi-drug resistant organisms

c. Adverse reactions

- **Hypersensitivity reactions**—it was thought that allergic cross-reaction between penicillins and cephalosporins was as high as 10%. However, in actuality, cross-reactivity is <2% and most patients who are allergic to cephalosporins are not allergic to penicillins
- Can suppress the gut flora and contribute to vitamin K deficiency, leading to bleeding diathesis
- Rash—morbilliform rash is the most common
- Encephalopathy or seizure fourth-generation cephalosporins especially)

d. Other features

- First-generation cephalosporins are used for surgical prophylaxis or mild cellulitis
- Many forms of cephalosporins must be administered intravenously. There are oral cephalosporins for the first-, second-, and third generations
- Cefuroxime and cefpodoxime are sometimes used to treat community-acquired pneumonia
- Cefoxitin can be used for abdominal infections, such as peritonitis
- Ceftriaxone can be given as an IM injection to treat gonorrhea. Intravenously it plays an important role in empiric treatment for meningitis

- Cephalosporins have a high association with antibiotic-induced *Clostridium difficile* infection
- Because of its broad coverage (including *Pseudomonas*), cefepime is a good choice for empiric therapy in nosocomial infections as well as febrile neutropenia
- Fifth-generation cephalosporins are currently approved to treat skin and soft tissue infections, including those caused by MRSA

e. Examples (list of examples is not exhaustive)

- First generation: cefazolin, cephalexin, cefadroxil
- Second generation: cefaclor, cefoxitin, cefuroxime, cefotetan, cefprozil
- Third generation: ceftriaxone, cefixime, cefotaxime, ceftazidime, cefdinir, cefpodoxime
- Fourth generation: cefepime is the only fourth-generation cephalosporin
- Fifth generation: ceftaroline, cefiderocol, ceftobiprole

3. **Miscellaneous cell wall inhibitors**

a. Vancomycin

- Inhibits cell wall synthesis by interfering with cross-linkage of peptidoglycan chains (different site of action from penicillin), also damages cell membranes
- Main use is to treat staphylococcal infections resistant to other β-lactams, such as MRSA, or if penicillin allergy is present; not used for gram-negative organisms
- Oral vancomycin is effective to treat *C. difficile* infections of the bowel (it is not systematically absorbed when administered orally)
- Acts synergistically with aminoglycosides to treat enterococcal infections
- Adverse reactions include fever, nephrotoxicity, ototoxicity, and **vancomycin infusion reaction** (VIR, previously called "red man syndrome"): flushing due to infusion-induced histamine release). Treat VIR by slowing the infusion and giving antihistamines (i.e., diphenhydramine)
- Serum levels must be followed to avoid nephrotoxicity, and doses must be adjusted for renal insufficiency
- Vancomycin resistance is an emerging, ominous phenomenon. Many enterococci have developed resistance to vancomycin

creating vancomycin-resistant enterococci (VRE)

Quick HIT

Treat MRSA with vancomycin. Treat MSSA with a penicillin such as oxacillin or nafcillin.

- Dalbavancin, oritavancin, and telavancin are newer long-acting parenteral agents with similar spectrum of activity as vancomycin (MRSA and other gram-positive organisms). They are noninferior to vancomycin for skin and soft tissue infections and can be used for patients who need parenteral therapy but who do not require inpatient treatment and have difficulty with medication adherence

b. Carbapenems

- Synthetic β-lactams designed to be more resistant to β-lactamases and penicillinases
- Examples include imipenem, ertapenem, doripenem, and meropenem
- Imipenem is always combined with cilastatin to prevent renal toxicity associated with the metabolism of imipenem
- Carbapenems have broad-spectrum antimicrobial coverage, including penicillin-resistant pneumococci, *Pseudomonas* (except ertapenem), anaerobes, and *Enterobacter* infections
- They are used empirically for patients in whom gram-negative sepsis is suspected
- They may cause nausea, vomiting, and sometimes neutropenia
- They can cause neurotoxicity and reduce the seizure threshold (especially imipenem)

c. Monobactams

- Aztreonam is currently the only available preparation in the United States
- Contains only one of the two structural rings found in other β-lactams, hence the name. It retains resistance to β-lactamases
- Narrow spectrum of activity: Primarily aerobic gram-negative rods, including ***Pseudomonas, Klebsiella***, and ***Serratia***
- Less cross-reactivity with penicillin than other β-lactam antibiotics makes it useful for patients with true penicillin hypersensitivity

who cannot undergo penicillin desensitization. Remains costly which precludes its broader use

d. β-Lactamase inhibitors
- Examples include sulbactam, tazobactam, avibactam, vaborbactam, and clavulanic acid
- Not used by themselves, but rather combined with penicillins, cephalosporins, or carbapenems to enhance antimicrobial activity (e.g., amoxicillin + clavulanic acid = Augmentin)

Quick HIT

Piperacillin and ticarcillin are always used in combination with a β-lactamase inhibitor (e.g., tazobactam, clavulanic acid).

e. Bacitracin
- Inhibits bacterial cell wall synthesis by inhibiting transport of peptidoglycans
- Effective against gram-positive organisms
- Used **topically** only (because it is so nephrotoxic)

B. Protein Synthesis Inhibitors

1. **Tetracycline**

a. Mechanism of action
- Inhibits protein synthesis by binding to 30 S subunit of bacterial ribosome
- **Bacteriostatic**

b. Antimicrobial coverage
- Effective against certain intracellular bacteria: Chlamydia, rickettsial diseases (e.g., Rocky Mountain spotted fever), mycoplasma, spirochetes
- Treats gram-negative *Vibrio cholerae*
- Also treats spirochete causing Lyme disease (*Borrelia burgdorferi*)
- Often used to treat uncomplicated respiratory tract infections such as sinusitis and bronchitis
- Tigecycline is broad-spectrum (including MRSA and VRE) and is able to evade the resistance mechanisms which render the other

tetracyclines less active

c. Adverse reactions
- GI—epigastric pain, nausea, vomiting
- **Deposits occur in calcified tissues** (e.g., teeth and bones of the fetus if given during pregnancy and potentially in any child <8 years old). This can result in permanent discoloration of teeth, stunting of growth, and skeletal deformities
- Phototoxicity
- Hepatotoxicity—is rare but can be fatal

d. Cautions
- Do not give to pregnant individuals or children <8 years old
- Do not give to patients with renal insufficiency (except doxycycline)
- Decreased absorption occurs if taken with milk and antacids
- Resistance is common

e. Examples
- Tetracycline
- Doxycycline
- Minocycline
- Tigecycline (newer antibiotic in a related class of drugs called glycylcyclines)
- Eravacycline (parenteral agent for complicated intra-abdominal infections)
- Omadacycline (newer agent for community-acquired pneumonia)

2. **Macrolides**

a. Mechanism of action
- Inhibit protein synthesis by binding to 50 S subunit of bacterial ribosome
- **Bacteriostatic** (may be bactericidal at high doses)

b. Antimicrobial coverage
- Good at treating intracellular pathogens, such as *Mycoplasma*, *Chlamydia*, and *Legionella*
- Erythromycin and clarithromycin have activity against methicillin-susceptible staphylococci and streptococci
- Clarithromycin is the treatment of choice for *Mycoplasma* pneumonia (“walking pneumonia”) and *Legionella* spp.

- Azithromycin or erythromycin are also appropriate alternatives to penicillin G if there is a penicillin allergy (e.g., treatment of chlamydia in pregnancy, to avoid tetracycline)
- Due to adverse events and frequent dosing, erythromycin is being used less often as an antibiotic. It is still used as a GI stimulant for its pro-motility effects
- Clarithromycin is one of the drugs used in therapy for eradication of *Helicobacter pylori*
- Azithromycin and clarithromycin have activity against *H. influenzae*
- Azithromycin also treats *Moraxella catarrhalis*

c. Adverse reactions
- GI side effects are the most common and include epigastric pain, nausea, and vomiting (particularly with erythromycin)
- Cholestasis
- Prolongation of QT interval, especially with erythromycin

d. Cautions
- Erythromycin should not be prescribed to patients with liver failure because it is metabolized in the liver
- Erythromycin and clarithromycin interact with many drugs due to their inhibitory effect on the P-450 system

e. Examples
- Azithromycin
- Clarithromycin
- Erythromycin

Quick HIT

Most common application of aminoglycosides for treating serious infections caused by aerobic gram-negative rods:
- Sepsis
- Complicated UTI
- Nosocomial respiratory tract infections
- Osteomyelitis
- Complicated intra-abdominal infections

3. **Aminoglycosides**

a. Mechanism of action
   - Inhibit protein synthesis by binding to 30 S subunit of bacterial ribosome
   - **Bactericidal**

b. Antimicrobial coverage
   - Treat gram-negative aerobes, such as *E. coli*, *Pseudomonas*, *Acinetobacter*, or *Klebsiella*. Used for empiric coverage for severe gram-negative infections when resistant organisms are suspected
   - Sometimes used in combination with ampicillin or other β-lactams for complicated UTIs, meningitis, or other serious infections
   - No activity against anaerobes

c. Adverse reactions
   - **Ototoxicity**—**may cause irreversible hearing loss**, especially if infused too quickly. Baseline and follow-up hearing tests are required for patients on aminoglycosides long term
   - **Nephrotoxicity**—may cause renal insufficiency or acute tubular necrosis. Aminoglycoside toxicity is dose-related, so be sure to adjust dose for renal dysfunction

d. Other points
   - Most are given parenterally
   - Check peak and trough levels to avoid drug toxicities
   - Often given in combination of other broad-spectrum antibiotics for critically ill patients. Once causative organism and susceptibilities is identified, aminoglycosides are usually switch to alternative agents due to their high toxicity profile

e. Examples
   - Gentamicin
   - Streptomycin
   - Tobramycin
   - Amikacin
   - Neomycin

4. **Miscellaneous protein synthesis inhibitors**

a. Clindamycin
   - Binds to 50 S subunit of ribosome, inhibiting bacterial protein synthesis

- Key feature is activity against anaerobic bacteria. In addition to anaerobes, can be used for streptococcal and staphylococcal infections (may be helpful to inhibit bacterial toxin production)
- It can also be used to treat many types of gram-positive cocci. If the patient is allergic to cephalexin, clindamycin can be given instead
- The most notable adverse effect is its potential to cause antibiotic-associated diarrhea, including *C. difficile* colitis

b. Chloramphenicol

- It binds to 50 S bacterial ribosomal subunit, but may also interfere with human ribosomal activity, and so it has the potential to be highly toxic
- Broad-spectrum antimicrobial coverage, including anaerobes and some rickettsial diseases (doxycycline is usually preferred but chloramphenicol can be used as a less optimal alternative); readily penetrates the CSF
- Adverse effects may be severe and even fatal: **aplastic anemia** and **gray syndrome** in infants (cyanosis due to respiratory depression and cardiovascular collapse)
- Inhibits the P-450 system, potentiating the effect of many important drugs

c. Linezolid

- Has great coverage of gram-positive bacteria, including streptococci, enterococci, and MRSA
- Most serious reported adverse effect is thrombocytopenia (monitor blood counts with prolonged therapy). Peripheral neuropathy has also been reported with extended treatment regimens
- Linezolid inhibits monoamine oxidase. This may lead to serotonin syndrome when given with pro-serotonin agents such as SSRIs
- Great oral bioavailability

C. Fluoroquinolones

1. Mechanism of action—direct inhibitors of bacterial DNA synthesis

   a. Inhibit bacterial DNA gyrase and topoisomerase IV, blocking replication of bacterial DNA

   b. **Bactericidal**

Quick HIT

Fluoroquinolones are only antimicrobial agents in clinical use that are direct inhibitors of bacterial DNA synthesis.

2. Antimicrobial coverage
   a. Have excellent activity against ***gram-negative organisms***, including *Pseudomonas, E. coli, Proteus, Legionella,* and *gonorrhea*. Gram-positive coverage is variable. Certain fluoroquinolones (e.g., levofloxacin, moxifloxacin) have good gram-positive coverage and are can be used for community-acquired pneumonia. Only moxifloxacin has anaerobic coverage
   b. Commonly used to treat UTIs. Ciprofloxacin also treats acute diarrhea due to enteric bacteria (traveler's diarrhea)
   c. Can be used for treatment of community-acquired pneumonia but are not the preferred agent due to high amount of adverse effects

Quick HIT

Best antibiotics for gram-negative rods (*E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*):
1. Cephalosporins (for Pseudomonas, only fourth generation)
2. Piperacillin-tazobactam
3. Carbapenems
4. Fluoroquinolones
5. Aminoglycosides
6. Aztreonam (if hypersensitivity with other agents)

3. Adverse reactions
   a. Cardiac—QT interval prolongation and possible association with aortic aneurysm and dissection
   b. GI—nausea, vomiting, diarrhea including *C. difficile* colitis
   c. CNS—dizziness, headache, lightheadedness, agitation, peripheral neuropathy
   d. Nephrotoxicity
   e. Hypoglycemia
   f. Cartilage damage in children has not been shown in humans, although animal studies suggest this

g. Tendinitis and tendon rupture
h. Cautions
   - There are many adverse effects of fluoroquinolones that limit their use to cases in which benefits clearly outweigh risks
   - Significantly reduced absorption if consumed with divalent cations, such as antacids that contain magnesium
   - Must be adjusted for renal insufficiency
   - Generally avoid in nursing mothers and children (although the latter is evolving, especially in children with cystic fibrosis)
   - Avoid in pregnant patients because animal studies show cartilage damage
i. Examples
   - Levofloxacin
   - Ciprofloxacin
   - Ofloxacin
   - Moxifloxacin

D. Antituberculosis Antibiotics

1. Principles of therapy
   a. **Never treat tuberculosis with only one antibiotic.** Use multidrug therapy because drug resistance is such a problem with *Mycobacterium tuberculosis.*
   b. Treat active tuberculosis with traditional four antibiotic regimen (isoniazid [INH], rifampin, pyrazinamide [PZA], and ethambutol) for 2 months, followed by rifampin and INH for 4 months. Alternative regimen is a 4-month shortened regimen of rifapentine and moxifloxacin.
   c. Since *M. tuberculosis* is a slow-growing organism, the required duration of treatment is longer than it is in other bacterial infections.
2. Important first-line antituberculosis agents (many second-line agents also exist)
   a. INH
      - Attacks the enzyme that produces the mycolic acids that comprise the mycobacterial cell walls.
      - Resistance to INH develops rapidly if it is used alone.
      - INH is used frequently in treatment of latent TB.

- The most important adverse reaction is **drug-induced hepatitis**, which can be fatal.
- It may cause a relative pyridoxine (vitamin B_6) deficiency, resulting in peripheral neuropathy. This is reversible with pyridoxine administration.

b. Rifampin

- Inhibits bacterial RNA synthesis by blocking RNA polymerase.
- In addition to its role as an antituberculosis agent, rifampin is used as prophylaxis for close contacts of patients with meningococcal meningitis.
- Rifampin is also active against *Mycobacterium leprae*, which causes leprosy.
- May stain tears or urine an orange-red color; induces hepatic microsomal enzymes and decreases the half-life of many medications.
- Rifampin is a powerful inducer of the cytochrome P-450 enzyme system, so drugs interactions should be monitored carefully.

c. PZA

- Inhibits fatty acid synthesis of even slow-growing *M. tuberculosis* at a different step than INH.
- Active against tubercle bacilli residing in macrophages.
- May cause hyperuricemia, resulting in a gouty attack.
- Potentially hepatotoxic

d. Ethambutol

- Inhibits an essential component of the mycobacterial cell wall.
- It may cause **optic neuritis,** resulting in diminished visual ability as well as red-green color blindness. Periodic visual testing may be necessary.
- It may also precipitate a gouty attack.
- Also used in the treatment of *Mycobacterium aviumintracellulare.*

E. Miscellaneous Antibiotics

1. Trimethoprim (TMP)

   a. TMP inhibits dihydrofolic acid reductase, blocking bacterial DNA synthesis.

   b. It works synergistically with sulfonamides.

c. TMP was formerly used alone to treat UTIs but now is most commonly used in combination with sulfamethoxazole (SMX). SMX inhibits a second, unique step in bacterial folate synthesis, creating a synergistic effect.
d. TMP/SMX is used both for prophylaxis and treatment of *Pneumocystis jirovecii.*
e. It may cause folate deficiency, resulting in megaloblastic anemia.
f. TMP/SMX is used to treat *S. aureus* (including some MRSA), UTIs, *Pneumocystis carinii* pneumonia, *Shigella,* and *Salmonella,* among other infections.
g. Side effects of TMP include hematologic (bone marrow suppression), renal (can cause both a benign rise in creatinine as it inhibits creatinine secretion, and a true acute kidney injury (AKI) if acute interstitial nephritis occurs), and hyperkalemia.

2. Sulfonamides
   a. Structural analogs of *p*-aminobenzoic acid that inhibit the enzyme dihydropteroate synthase, which is necessary for folic acid, and thus DNA synthesis.
   b. Treat both gram-positive and gram-negative bacteria, although resistance to sulfonamides is increasingly common.
   c. Most sulfonamides that were once used alone have been replaced by the combination of TMP/SMX.
   d. Some forms of sulfonamides are still given as monotherapy, such as silver sulfadiazine (topical solution) in burn patients to prevent infection, and sodium sulfacetamide (ophthalmic ointment) for bacterial conjunctivitis.
   e. The most common adverse reactions are rash, photosensitivity, nausea, vomiting, and diarrhea.
   f. A rare but dreaded associated adverse reaction is **Stevens–Johnson syndrome.**
   g. **Do not give to patients with G6PD deficiency because they can precipitate a hemolytic response.**
3. Metronidazole
   a. Forms a cytotoxic compound through an oxidation–reduction action which damages DNA. Bactericidal.
   b. Effective against anaerobic bacteria as well as certain protozoal organisms such as *Entamoeba histolytica, Giardia,* and

Trichomonas.

c. Oral form very useful in the treatment of *C. difficile* diarrheal infections.

d. Adverse effects—may result in a **disulfiram-like reaction** if consumed with alcohol. If used long-term, can cause peripheral neuropathy. May also cause headache and a metallic taste. Hepatitis and pancreatitis are extremely rare. Warfarin effects are enhanced with concomitant use of metronidazole due to inhibition of warfarin metabolism—warfarin levels should be closely monitored.

4. Nitrofurantoin

a. Works by a complex mechanism to inactivate several bacterial enzyme systems including acetyl CoA.

b. Primary use is for **uncomplicated** lower urinary tract infections caused by *E. coli* or other common community-acquired organisms. Do not use for pyelonephritis or infections outside of the urinary system.

5. Table A-1 lists mechanisms of action, uses, and adverse reactions for important antibiotics.

***Quick* HIT**

- S_1 = mitral valve closure
- S_2 = aortic valve closure (pulmonic valve closure contributes)

***Quick* HIT**

- Aortic area = right second intercostal space close to sternum
- Pulmonic area = left second intercostal space close to sternum
- Tricuspid area = left fourth and fifth intercostal space
- Mitral area = apex

Physical Examination Pearls

Heart Sounds

A. For murmur of mitral stenosis and to hear S_3 and S_4, use the bell of the stethoscope.

B. For pericardial friction rubs, aortic/mitral regurgitation murmurs, and to hear S_1 and S_2, use the diaphragm of the stethoscope.

C. Ventricular systole takes place between S_1 and S_2, and ventricular diastole between S_2 and S_1. Remember that diastole lasts longer than systole; this distinction makes it easy to identify the two sounds.

D. How to differentiate S_3 and S_4 (the lines represent duration of pause between sounds): S_3 comes immediately after S_2, and S_4 comes immediately before S1.

1. S_1—S_2–S_3
2. S_4–S_1—S_2

E. Splitting of S_2 during inspiration and paradoxical splitting of S_2.

1. The second heart sound has two parts: Aortic valve closure, then pulmonic valve closure.
2. With inspiration, there is increased blood return to the right heart. This increased flow delays pulmonary valve closure, which results in the normal splitting of S_2 during inspiration.
3. Paradoxical splitting of S_2 refers to the narrowing of this split during inspiration (instead of the normal widening that occurs). This can occur as a result of delayed aortic closure (as seen in LBBB, aortic stenosis, and hypertension).

F. It is easier to hear S_3, S_4, and murmur of mitral stenosis if the patient is lying on their left side. Use the bell of the stethoscope and apply light

pressure at the apical impulse. S_3 disappears if a lot of pressure is applied.

Murmurs

A. Grade 1 —very faint; barely detectable

B. Grade 2 —quiet

C. Grade 3 —moderately loud without a thrill

D. Grade 4 —loud; associated with a palpable thrill

E. Grade 5 —very loud; can hear it with stethoscope partially off the chest

F. Grade 6 —heard with stethoscope entirely off the chest

Breath Sounds

A. Vesicular Breath Sounds

1. Soft, low-pitched (air moving through small airways)
2. Audible throughout most lung fields
3. Heard during all of inspiration and first third of expiration

B. Bronchial Breath Sounds

1. Loud, high-pitched (air moving through large airways)
2. Longer expiratory than inspiratory phase (opposite of vesicular sounds)
3. Hear a gap between inspiration and expiration
4. Heard in central areas (over trachea)
5. Bronchial sounds are abnormal if heard over the peripheral lung areas (where only vesicular sounds should be heard). This suggests an area of consolidation

C. Bronchovesicular Sounds

1. Intermediate pitch
2. Equal duration of inspiratory and expiratory phases

D. Adventitious Breath Sounds

1. Rales (also called crackles)
   a. Can be heard during inspiration or expiration; intermittent (discontinuous) sounds
   b. Usually due to excessive fluid in the lungs or atelectasis
   c. Causes include pneumonia, CHF, interstitial lung disease (usually dry, "Velcro-like" crackles)
   d. Sometimes differentiated based on sound—fine crackles are high-pitched, soft, and brief in duration; coarse crackles are lower-pitched, louder, and longer in duration
2. Wheezes have a hissing or musical sound caused by air moving through narrowed airways. Asthma is the most common cause
3. Rhonchi have a snoring quality and lower pitch, and are due to high mucus production in the large airways (e.g., chronic bronchitis)

Abdominal Examination

A. Inspect —look for scars.

B. Auscultate —listen to bowel sounds; this is a nonspecific part of the abdominal examination.

C. Palpate —feel all quadrants, then palpate more deeply in all quadrants.

1. Is the abdomen soft? A rigid abdomen may be a sign of a perforated viscus or peritoneal inflammation (acute abdomen).
2. Check for tenderness in all quadrants.
3. Check for rebound tenderness—does it hurt when you push down or let go? Pain on withdrawal of the hand is **rebound tenderness** and suggests peritoneal inflammation.

4. Is there guarding? **Guarding** refers to an area of rigidity and is significant when it is involuntary (i.e., not due to voluntary muscular contraction). To prevent voluntary guarding, one tip is to have the patient bend their knees while keeping their feet on the bed—this relaxes the abdominal wall muscles.

Neurologic Examination

A. Evaluate the Following:

1. Level of consciousness, speech fluency
2. Pupillary size and reactivity, extraocular muscle movement—give information about function of the brainstem, especially CNs III and VI
3. Complete cranial nerve examination
4. Muscle strength testing (be sure to test both proximal and distal muscle groups in each limb)
5. Truncal ataxia, pronator drift of arm (sensitive test of motor weakness)
6. Sensation
7. Cerebellar testing—finger to nose, heel to shin, and rapid alternating movements; test gait on ambulation, heel-to-toe walking is good for detecting mild ataxia
8. Deep tendon reflexes—asymmetry suggests corticospinal tract dysfunction (upper motor neuron lesion)
9. Babinski sign—toes should normally flex. If they extend, this is a positive Babinski sign

Quick HIT

If you cannot elicit lower extremity reflexes, have the patient lock the fingers and pull their arms apart (to distract them) as you try again.

B. Upper and Lower Motor Neuron Defects (see Table A-2)

1. Deep tendon reflexes
   a. Grading of reflexes
      - 0 = No reflex
      - 1 = Diminished reflexes

- 2 = Normal
- 3 = Increased reflexes
- 4 = Hyperactive reflexes

b. Locations

- Biceps (C5)
- Brachioradialis (C6)
- Triceps (C7)
- Patellar (knee jerk) (L4)
- Ankle (S_1)

c. Muscle strength

- 0 = No contraction
- 1 = Flicker of contraction (muscle is “firing”)
- 2 = Moves limb when gravity is eliminated
- 3 = Moves limb against gravity (but not against any resistance)
- 4 = Moves limb against gravity and some resistance
- 5 = Normal muscle strength; moves limb against maximal resistance

C. Palpation of Lymph Nodes (Figure A-2)

Tumor Markers

Tumor markers and the cancers they differentiate, as well as their usefulness, are covered in Table A-3.

TABLE A-2 Upper Versus Lower Motor Neuron Defects

Upper Motor Neuron Signs	Lower Motor Neuron Signs
Spasticity	Flaccid paralysis
Increased deep tendon reflexes (hyperreflexia)	Decreased deep tendon reflexes
Babinski reflex (plantar response extensor)—toes upward (abnormal)	No Babinski reflex (plantar response flexor)—toe downward (normal)
No atrophy	Muscle atrophy
No fasciculations	Fasciculations present

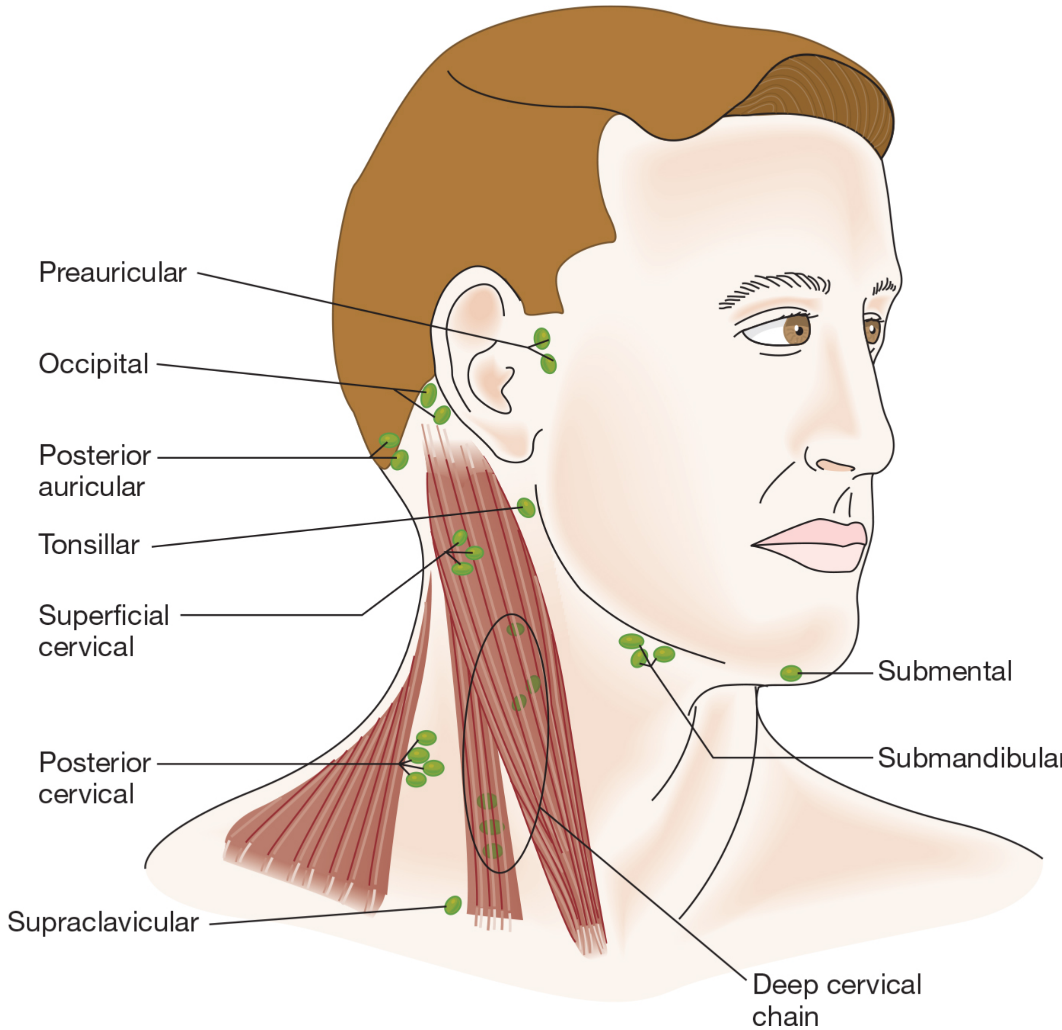


FIGURE A-2 **Palpation of the lymph nodes in a physical examination.**
(Reprinted with permission from Bickley LS, Szilagyi PG. *Bates' Guide to Physical Examination and History Taking*. 8th ed. Lippincott Williams & Wilkins; 2003:203.)

Workup and Management of Common Problems

On the Wards

Refer to respective sections in each chapter for a more thorough discussion.

Hypotension

A. Causes: All causes of shock including distributive (sepsis, anaphylaxis, neurogenic), hypovolemic, cardiogenic, or obstructive (cardiac tamponade, large PE). Other common culprits are medication (β-blockers, calcium channel blockers, nitrates, opioids, sedatives, epidural infusion)

B. Management

1. Quickly assess mental status—how symptomatic is the patient?
2. Obtain a full set of vitals, including BP in both arms. Expect a compensatory tachycardia unless masked by nodal blocking medications. Bradycardia may result in reduced cardiac output.
3. Determine baseline BP (may not be significantly different).
4. Consider ECG, CXR, arterial blood gas (ABG), blood culture (if febrile), and CBC (if infection or bleeding is suspected, but keep in mind hemoglobin may not yet have equilibrated if bleeding is recent).
5. Treatment should be directed toward the cause.
6. If patient is symptomatic, the reverse Trendelenburg position may be helpful.
7. Consider crystalloid bolus (500 mL or 1 L or normal saline or lactated Ringer's)—repeat this if BP does not improve (but be careful in patients with CHF, dialysis dependence, or cardiogenic shock).
8. Discontinue or hold antihypertensive medications.
9. Vasopressors may be needed if there is insufficient response to IV fluids.
10. If hypotension is profound or persists despite fluid therapy, consider transferring the patient to the ICU.
11. Put the patient on a cardiac monitor.

TABLE A-3 Tumor Markers

Tumor Marker	Cancer	Limitations	Uses/Comments
CEA	Colorectal cancer	Poor sensitivity and specificity—this is not an effective screening test; levels may be elevated in other malignancies and in some nonmalignant diseases	• Effective for monitoring disease process—a decrease in CEA indicates a favorable response to treatment, and an increase in CEA indicates disease progression • Prognosis—the risk of recurrence is higher if the CEA level was elevated before surgery
AFP	HCC and nonseminomatous germ cell tumors of testis (NSGCT)	Not specific; can be elevated in nonmalignant diseases such as cirrhosis and hepatitis	Highly elevated AFP levels are present almost exclusively in primary HCC and NSGCT of the testis
CA-125	Ovarian cancer	Poor sensitivity and specificity for ovarian cancer, not useful for screening—a normal CA-125 does not exclude ovarian cancer	• Very useful for monitoring response to treatment–a decrease in CA-125 after treatment indicates shrinkage of the tumor, and an increase indicates disease progression or recurrence • Between 80% and 90% of women 50 yrs of age with a pelvic mass and an increased CA-125 will be found to have ovarian cancer
Prostate-specific antigen (PSA)	See prostate section		
CA 19-9	Pancreatic cancer	Low specificity—this is elevated in colorectal, pancreatic, and gastric cancer, as well as pancreatitis and ulcerative colitis	73% of patients with pancreatic cancer have CA 19-9 levels greater than 100 U/mL

β-hCG	Gestational trophoblastic disease, gonadal germ cell tumor	Elevated in pregnancy	• This has a high sensitivity for diagnosis of choriocarcinoma and trophoblastic neoplasm after evacuation of a molar pregnancy • Either hCG or AFP is elevated in 90% of patients with NSGCT of the testis • hCG may be elevated in either seminomatous germ cell tumors or NSGCTs, but AFP is only elevated in NSGCTs

Hypertension

A. Causes

1. Failure to administer, order, or take antihypertensive medications
2. Pain, agitation
3. Hypertensive emergencies (manifested by MI, aortic dissection, encephalopathy, hemorrhagic stroke, or acute CHF exacerbation)
4. Delirium tremens or alcohol/benzodiazepine withdrawal
5. Eclampsia or preeclampsia
6. Cocaine, amphetamine use

Quick HIT

With hypotension or hypertension, treat the patient, not the BP reading. Asymptomatic patients with hypotension often do not require treatment. Likewise, severe asymptomatic hypertension (previously known as hypertensive urgency) can often be managed with observation or with resumption of oral antihypertensives.

B. Management

1. Always recheck the BP with a properly fitting cuff to confirm HTN. Check other vital signs.
2. Check the patient's medication record to ensure appropriate adherence with therapy.

3. Check for signs of end-organ damage due to HTN, which indicate that a hypertensive emergency is occurring: chest pain/ECG changes, neurologic examination findings/encephalopathy, acute renal insufficiency or failure, papilledema.
4. Consider the following tests as appropriate, given the presentation: ECG, renal function panel, cardiac enzymes, CXR, CT of the head.
5. Treat pain and agitation as needed.
6. If HTN is mild and the patient is asymptomatic, observation with follow-up may be appropriate.
7. Oral antihypertensive medications (e.g., α-blockers, calcium channel blockers, ACE inhibitors/ARBs, or oral β-blockers) can be given for most cases of hypertension. Follow response and repeat medication as needed. Be careful not to overtreat hypertension, especially when long standing.
8. **Never ignore symptomatic HTN or hypertensive emergencies.** BP must be reduced quickly but carefully. (Reduce mean arterial pressure by no more than 25% in the first 2 hours.) This should be done in the ICU, with IV labetalol, nitroprusside, or enalaprilat, or additional doses of the patient's current regimen.
9. Reduce or discontinue IV fluids if volume overload is suspected.

***Quick* HIT**

Be careful not to lower BP too quickly in a hypertensive patient unless another emergency is present that requires rapid lowering of BP such as aortic dissection or intracranial hemorrhage.

Chest Pain

A. Causes

1. **Heart/vascular:** Angina, MI, pericarditis, aortic dissection
2. **GI:** Gastroesophageal reflux disease, diffuse esophageal spasm, esophageal tear or rupture, peptic ulcer disease, gallbladder disease, acute cholecystitis
3. **Chest wall:** Costochondritis, rib fracture, muscle strain, herpes zoster
4. **Psychiatric:** Anxiety, somatization

5. **Pulmonary:** PE, pneumothorax, pleuritis
6. **Stimulant use:** Can cause angina or MI

B. Management

1. As always, check vital signs. In most cases, obtain a 12-lead ECG. Compare with an old ECG. Get more information about the patient's cardiac history and current history of chest pain (concerning for cardiac ischemia if worsens with exertion, radiates to arms, or associated with diaphoresis, nausea, or vomiting).
2. Order ECG and cardiac enzymes (troponin) × 3, every 4 to 8 hours, if acute coronary syndrome is suspected. Obtain ECG more frequently (as often as every few minutes) if ongoing chest pain or dynamic ECG changes.
3. Consider CXR (pneumothorax, widened mediastinum, pleural effusion). Consider ABG or CT scan/scan if PE is suspected.
4. If acute coronary syndrome is suspected:
   a. Supplemental oxygen if $SpO_2 < 90\%$, titrate up as needed.
   b. Nitroglycerin (sublingual) for pain; if pain continues, can give opioids or nitroglycerin IV infusion until free of chest pain. Nitroglycerin is contraindicated in suspected right ventricular infarction or if patient took a PDE-5 inhibitor (such as sildenafil) in last 24 hours.
   c. Keep systolic BP >90 mm Hg.
   d. Antiplatelet therapy
      i. Aspirin
      ii. $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticagrelor, etc.)
   e. Anticoagulant therapy
      i. Heparin—give a loading dose, then start a drip. Check the PTT at baseline and in 6 hours. Ensure there are no contraindications to anticoagulation prior to starting (recent intracranial hemorrhage, active bleeding).
   f. High-intensity statin within first 24 hours
   g. Put the patient on a cardiac monitor, and consider transfer to a cardiac care unit or to a center capable of performing percutaneous coronary intervention (PCI).

5. Treat other suspected conditions appropriately. See discussions of PE, aortic dissection, pneumothorax, GERD, and PUD.

Tachycardia

A. Types: Determine whether the tachycardia is a narrow or wide complex. Obtain an ECG—is it regular? If wide, treat like ventricular tachycardia (VT). If narrow, determine whether the tachycardia is sinus or non-sinus.

B. Sinus Tachycardia

1. HR >100, hardly ever >200 beats/min.
2. Sinus P waves precede each QRS complex and P waves are upright in lead II.
3. Causes include pain, exercise, hypovolemia (dehydration or bleeding), PE, hyperthyroidism, fever/inflammation, anemia, anxiety, panic attacks, decongestants, β-agonists, and substance use or withdrawal.
4. Treat the underlying cause. In older patients with cardiac disease, consider a β-blocker to prevent the increase in myocardial O_2 demand that occurs at a high HR. Never start a β-blocker to "treat the tachycardia" unless you have ruled out all serious causes above.

C. Narrow Complex Non-Sinus Tachycardia

1. Also known as supraventricular tachycardias (SVT). May be due to atrial flutter, atrial fibrillation, AV reentrant tachycardia (AVRT), or AV nodal reentrant tachycardia (AVNRT).
2. Treatments vary according to the arrhythmia and presence of instability.
   a. If any unstable SVT (hypotension, altered mental status, ischemic chest pain, or SOB), synchronized cardioversion is recommended treatment.
   b. AVRT or AVNRT—treat with vagal maneuvers or IV adenosine. Prior to any treatment, ensure patient is on a cardiac monitor and the crash cart is at bedside. AV nodal blockers may also be used.
   c. Atrial fibrillation—control the rate with a β-blocker, DC cardioversion, anticoagulation.

d. Atrial flutter—treat as with atrial fibrillation.
e. VT—if the patient is stable, give IV amiodarone. If the patient is unstable, perform DC cardioversion.

D. Wide Complex Tachycardia

1. Either ventricular tachycardia (VT) or SVT with aberration (early reentrant pathway)
2. Treat all wide complex tachycardias as VT unless proven otherwise. The probability of a WCT being VT is even higher if the patient has a history of ischemic heart disease. If patient is stable, give antiarrhythmics such as IV amiodarone. If the patient is unstable, perform immediate cardioversion.
3. Ventricular fibrillation—perform immediate defibrillation and CPR.

Oliguria

A. Typically Defined as Urine Output <500 mL/day or <0.3 mL/kg/hour

B. Causes

1. Not all AKI is oliguric. Causes for oliguria mirror causes of AKI.
2. Prerenal: hypotension, hypovolemia, cardiorenal syndrome, hepatorenal syndrome, renal arterial occlusion.
3. Renal: glomerulonephritis, acute tubular necrosis, acute interstitial nephritis, vascular insult, and so on.
4. Postrenal: obstruction of lower or upper (bilateral) urinary tract.

C. Management

1. Check vital signs.
2. Inquire about potential precipitating factors—for example, recent IV contrast administration (although it is controversial whether contrast-induced nephropathy is as common as once thought) new medications (NSAIDs, ACE inhibitors, antibiotics), surgery, recent intake and output, other comorbid conditions (e.g., sepsis, CHF).

3. Palpate the bladder, check a post-void residual, and consider insertion of a Foley catheter if obstruction is suspected. If the patient already has a Foley catheter, flush it with 20 to 30 mL of saline to make sure it is not clogged. If urine flows after the Foley placement or flushing, obstruction was most likely the cause.
4. If clinical syndrome or history is consistent with hypovolemia, trial a bolus of IV crystalloid fluid (NS or LR) and monitor for improvement.
5. If etiology remains unclear, order serum and urine chemistries and a renal function panel. Calculate the fractional excretion of sodium (FeNa <1% is consistent with prerenal causes). If the patient is on diuretics, calculate the fractional excretion of urea (as the FeNa is no longer reliable). Note that there are multiple etiologies of AKI with FeNa <1%, so this is not always clear cut.
6. Consider a renal ultrasound to exclude hydronephrosis.
7. If CHF and cardiorenal syndrome is suspected, consider diuresis (e.g., furosemide 20 to 60 mg IV).
8. Stop offending agents (nephrotoxic drugs).
9. Treat electrolyte disturbances and acid–base derangements, and determine if there is an indication for dialysis (Table A-4).

TABLE A-4 Indications for Urgent Dialysis: "AEIOU"

A: Acidosis with pH ≤7.1
E: Electrolyte derangements (hyperkalemia at any level with cardiac conduction abnormalities, K ≥6.5 mEq/L, or K ≥5.5 mEq/L with ongoing tissue breakdown)
I: Intoxication (acute poisoning)
O: Overload (pulmonary edema)
U: Uremia (signs including pericarditis, otherwise unexplained decline in mental status)

Fever in the Hospitalized Patient

A. Causes

1. Infection: have a systematic approach to consider the following:

a. Devices: central lines, peripheral IVs, Foley catheter, other indwelling devices
b. Nosocomial infection: hospital-acquired pneumonia, UTI, pressure wounds, surgical site infection, *C. difficile* colitis
c. Other infections: skin and soft tissue infection, pneumonia, UTI, bacteremia, endocarditis, GI tract infection (e.g., acute cholecystitis), septic arthritis, meningitis

2. Noninfectious causes: PE/DVT, medications (especially antibiotics), neoplasms, connective tissue disorders, postoperative inflammatory state.

B. Diagnosis

1. Check vital signs (tachycardia is an expected physiologic response to fever). Screen for sepsis criteria (tachycardia, fever, elevated WBC count, tachypnea) and treat accordingly.
2. Evaluate for signs and symptoms of localizing disease—for example, cough, abdominal pain, dysuria, meningeal signs, joint pain, diarrhea, rash, erythema, or drainage from wounds or devices.
3. Consider CBC, CXR, cultures (blood from two different sites and from any indwelling lines or ports, urinalysis and/or culture, sputum, any fluid collections), with sensitivity panels.
4. Lumbar puncture if meningitis is a possible cause; CT of the abdomen and pelvis if intra-abdominal infection is suspected.

C. Therapies

1. Acetaminophen is appropriate for symptomatic relief in most cases.
2. If the patient is ill-appearing, hemodynamically unstable or neutropenic, start broad-spectrum antimicrobial treatment empirically after cultures are obtained. Transfer to an ICU if patient is in septic shock.
3. If the patient is on an antibiotic and fever recurs, consider adding another antibiotic or changing the antibiotic altogether. Note that fevers may recur in the first 24 hours of starting appropriate antimicrobial therapy. Antifungal agents may be required.
4. Remove or replace indwelling IV lines and catheters. Send the tips of central lines for bacterial and/or fungal culture.

5. If no signs of infection and patient is hemodynamically stable, treat underlying etiology or continue diagnostic workup.

Hypoglycemia

- Two categories: too much insulin or not enough glucagon
- Too much insulin: iatrogenic insulin administration, oral diabetes medications with hypoglycemic effect (e.g., sulfonylurea), insulinoma (rare)
- Not enough glucagon: poor nutritional status, advanced liver disease
- If the patient can drink and hypoglycemia is mild, give juice. Consider giving 50 mL of D50W intravenously if the patient is symptomatic. After immediate correction of hypoglycemia, if patient can eat it is ideal to give carbohydrates with protein and fat (e.g., peanut butter with crackers) to sustain normoglycemia
- If the patient is NPO or hypoglycemia persists, start D5W or D10W maintenance fluids Titrate rate to achieve normoglycemia while avoiding fluid overload
- If there is no IV access and the patient cannot drink/eat, give glucagon (0.5 to 1.0 mg SC or IM)
- Review and modify insulin and oral diabetes medication regimens

Change in Mental Status (Acute Encephalopathy)

A. Causes

1. **Medications and intoxications:** sedatives, opioids, insulin, oral diabetes medications, H_2-blockers, TCAs, anticholinergics, corticosteroids, hallucinogens, cocaine, alcohol, methanol, ethylene glycol
2. **Hypoxia**—very common
3. **Hospital or postoperative delirium**—frequently compounded by medications
4. **Hypotension**—with reduced cerebral perfusion
5. **Substance intoxication or withdrawal**—for example, alcohol, benzodiazepines

6. **Hypercarbia/hypercapnea**
7. **Infection—**sepsis, PNA, UTI, SSTI, CNS infection, etc.
8. **Trauma**—head trauma, burns
9. **Metabolic disturbances**—acidosis, hypoglycemia, hypo/hypernatremia, hypercalcemia, hypo/hypermagnesemia, ammonia (acute liver failure or hepatic encephalopathy)
10. **Hyperthyroidism or hypothyroidism, thyroid storm**
11. **Neurologic causes**—stroke, subarachnoid hemorrhage, increased ICP, subclinical seizure
12. **Dehydration and malnutrition**—deficiencies of thiamine, vitamin B_{12}
13. **ICU delirium**—sundowning

B. Management

1. Determine if there is a baseline history of neurocognitive disorder or dementia—any recent fall?
2. Check vitals; perform a focused examination (including neurologic examination and mental status). Checking for inattention is helpful to assess for delirium (can use the CAM-ICU score)
3. Consider oxygen saturation ("pulse ox"), ABG, electrolytes, finger stick, CXR, blood cultures, hepatic panel, urine toxicology screen if a toxidrome is suspected
4. Consider a CT of the head to rule out stroke or intracranial mass or bleed
5. Correct reversible causes and stop offending medications (if possible)
6. Consider naloxone (dose starts at 0.04 mg IV, titrate up to target a normal respiratory rate of 12 breaths/min; for patients in cardiopulmonary arrest from opioid overdose start at 2mg IV), dextrose (D50), and supplemental oxygen
7. If patient is combative or is pulling out IVs, consider antipsychotics for emergency agitation or possibly restraints if necessary for patient/staff safety
8. Consider spot EEG to evaluate for subclinical seizure

Shortness of Breath/Acute Hypoxia

A. Causes

1. Pulmonary: pneumonia, PE, bronchospasm, pleural effusion, pulmonary edema, pneumothorax, obstruction (asthma/COPD), aspiration
2. Cardiac: CHF exacerbation, MI, arrhythmia, cardiac tamponade
3. Blood: severe anemia, "bad blood" (e.g., carboxyhemoglobin, methemoglobinemia)
4. Acid–base: metabolic acidosis with respiratory compensation, primary respiratory alkalosis
5. Other causes: rib fracture or chest wall pain (splinting), anxiety, panic attack

Quick HIT

Case-control studies and cohort studies are often referred to as "observational studies."

B. Management

1. Perform pulse oximetry immediately. If low, or if the patient appears ill, obtain an ABG and give supplemental oxygen (titrate according to response). Consider bilevel positive airway pressure in cases of COPD or CHF exacerbation if no contraindications.
2. Remember ABCs—intubate if necessary.
3. Consider bronchodilators, diuretics, and naloxone as appropriate.
4. Perform portable CXR immediately unless hypoxia is readily resolved.
5. Consider ECG, CBC (anemia, infection); scan (CTA chest) if PE suspected.
6. Consider anxiolytics if anxiety-related hyperventilation is suspected (after ruling out all other causes) and the patient is stable.

Quick HIT

Randomization is important because it leaves patient assignment to either experimental or control group completely to **chance.** When any element of human intrusion or judgment enters the process of patient assignment, bias is introduced.

Basic Statistics and Evidence-Based Medicine

A. Evidence-Based Medicine has been defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sacket D. *BMJ*. 1996;312:71).

B. Types of Research Studies

1. Case series—these may describe the results of a specific treatment, determine long-term outcome of a treatment or procedure, or describe the complication rates of a procedure or the natural history of a disease (see also Clinical Pearls A-1 and A-2)
   a. Size of a case series can range from two or three patients to thousands of patients. A case report is the description of a rare or interesting case
   b. Major disadvantage is the lack of a comparison group so one cannot reach definitive conclusions about treatment efficacy. Case series are prone to many biases
   c. Very common in surgical research

Quick HIT

Hierarchy of evidence (from highest to lowest)

1. Meta-analysis of randomized controlled trials
2. Randomized controlled trials
3. Cohort studies
4. Case-control studies
5. Case series
6. Expert opinion

Quick HIT

The basic difference between a randomized controlled trial and a prospective cohort study is the manner in which patients are assigned to either group.

- In a randomized controlled trial, patients are assigned to either the experimental or control group randomly, without input from physician or patient.
- In a cohort study, the treatment decision is not random and is determined by the recommendations of the physician, as well as the wishes of the patient, among other factors.

2. Cross-sectional studies—subjects are studied at a specific point in time ("snapshot" of a population)
3. Case-control studies
   a. Patients are selected because they have a certain outcome, and their history is retrospectively reviewed to identify exposures or risk factors that may be associated with that outcome. These are associations with that outcome but may not be causative
   b. By definition, case-control studies can be only retrospective
   c. Good for rare diseases and for diseases with long latent periods
   d. Very susceptible to bias because both exposure and disease development occurred prior to initiation of the study

CLINICAL PEARL A-1

Consolidation of Standards for Reporting Trials (CONSORT) Statement

- Published in 1996, revised in 2001 (*JAMA*. 2001; 285:1987).
- Twenty-one–point checklist of essential items that randomized controlled trial reports should include to facilitate their appraisal and interpretation.
- Many journals have endorsed CONSORT, but the rigor of enforcement varies.

CLINICAL PEARL A-2

Cochrane Library (www.cochrane.org)

- Regularly updated evidence-based medicine database
- Includes randomized controlled trials and systematic reviews in all specialties of medicine to determine how strong the evidence is for various medical treatments
- Consists of an international network of researchers and physicians who gather and evaluate the evidence in medical research

4. Cohort studies
    a. Subjects are selected according to exposure (e.g., a new medication, a procedure) and are followed over time to observe the development or progression of disease
    b. Cohort studies can be prospective or retrospective
    c. Prospective cohort studies follow patients over time to observe a certain outcome, but patient assignment into the two treatment groups is not randomized, so confounding variables may be unequally distributed (see later)
5. Randomized controlled trial
    a. A type of cohort study involving a control group and an intervention group
    b. Patient assignment into either group is left completely to chance (if properly done). Therefore, known and unknown confounders are likely to be equally distributed

c. Methodologically superior to other study designs because it is least susceptible to bias

6. Meta-analyses
   a. Meta-analyses combine data from several individual studies to estimate an overall effect
   b. The strength of a meta-analysis is only as good as the quality of the primary studies it analyzes (e.g., a meta-analysis of 14 flawed, biased studies will produce a biased estimate of effect)
   c. A meta-analysis of well-conducted randomized controlled trials is the highest level of evidence

Quick HIT

The null hypothesis postulates that there is no difference between two groups. This hypothesis is either rejected or not rejected by a study.

Quick HIT

Clinical significance is unrelated to statistical significance. A study may obtain statistical significance for differences that have no clinical significance (e.g., 41% vs. 42% infection rate for two groups). With a large enough sample size, any study will obtain statistical significance.

C. Sensitivity and Specificity

1. Sensitivity = a/(a + c) (see Table A-5). Tests with high sensitivity are used for screening. They may yield false-positive results but do not miss people with the disease (low false-negative rate).
2. Specificity = d/(b + d). Tests with high specificity are used for disease confirmation.
3. Positive predictive value (PPV) = a/(a + b).
   a. If the test is positive, what is the probability that the patient has the disease?
   b. PPV depends on the prevalence (the higher the prevalence, the greater the PPV) and the sensitivity/specificity of the test (e.g., an overly sensitive test yields more false-positive results and has a lower PPV).

4. Negative predictive value (NPV) = d/(c + d).
   a. If test is negative, what is the probability that patient does not have the disease? **A high NPV is very important for a screening test.**
   b. NPV also depends on prevalence of disease (higher prevalence = lower NPV) and the sensitivity/specificity of the test (the more sensitive the test, the fewer the number of false-negative results, and the higher the NPV).

Quick HIT

If a study has a power of 80%, this means that if a difference of a particular stated magnitude exists between groups, there is an 80% chance of correctly detecting it.

Quick HIT

The lack of statistical power (i.e., sample size too small) invalidates a study because it can lead to statistical insignificance when there actually is a clinically meaningful difference.

D. Type 1 and 2 Errors

1. Type 1 (α) error: Null hypothesis is rejected even though it is true (false-positive finding).
   a. *P*-value is the chance of a type 1 error occurring.
   b. If the *P*-value is $\leq .05$, it is unlikely that a type 1 error has been made (i.e., a type 1 error is made five or fewer times out of 100 attempts).
2. Type 2 (β) error: Null hypothesis is not rejected even though it is false (a false-negative finding).
   a. A type 2 error results when the *P*-value fails to reach statistical significance **even though the groups being compared are truly different.** A type 2 error usually occurs when sample size is too small.
   b. The likelihood of avoiding a type 2 error is termed the **statistical power** of a study.

TABLE A-5 Sensitivity and Specificity

	Result of Test Under Investigation	
Result of Gold Standard	**Disease Positive**	**Disease Negative**
Test positive (a 1 b)	True positive (a)	False positive (b)
Test negative (c 1 d)	False negative (c)	True negative (d)

E. Statistical Power

1. A study with “negative” result (no difference between groups) must have adequate power to detect clinically meaningful differences.
2. Conventionally, a β-error rate of 20% is chosen, which corresponds with a study power of 80%. A study power of less than 80% is believed to have an unacceptably high risk of false-negative results (i.e., a study found no difference between two groups, when there actually was a difference).
3. Factors that affect the power of a study.
   a. Sample size—when sample size is small, a study is susceptible to type 2 error, which is why sample size calculation is done prior to the study being initiated.
   b. Level of statistical significance—conventionally, a *P*-value of .05 is chosen, although this is somewhat arbitrary.
   c. Variability of the sample data—the lower the variability, the fewer subjects are needed to demonstrate significant differences if they do indeed exist.
   d. Effect size chosen by researcher—this is based on pre-existing data and clinical judgment and is beyond the scope of this discussion.

Quick HIT

Think of the CI as a weather forecast: a vague forecast of “warm with possibility of rain” (this is a “wide” CI) is more likely to hold true but is not very precise. However, a forecast of “70 degrees with 30% chance of rain” (narrow CI) is much more precise but has a lower likelihood of holding true.

F. Confidence Interval

1. The confidence interval (CI) allows the reader to apply the results of a study to the "true" population from which the sample in the study was taken.
2. The most common CI is 95%, which means that the CI (i.e., the range) reported in the study holds true for 95 of 100 samples similar to the one in the study.
3. A "wider" CI increases the certainty of the estimate (i.e., it is more likely that the population from which the sample was selected would fall within the reported interval), but lowers its precision (see Quick Hit). A very wide CI should be interpreted with caution (a larger sample size may be needed to maintain power).
4. The larger the CI, the less power a study has to detect differences between two groups. The width of the CI depends on sample size; the larger the sample size (more likely to have power), the narrower the CI.

Quick HIT

Selection bias refers to differences in characteristics of subjects included/excluded or differences between selected comparison groups.

G. Association Versus Correlation

1. Association is used for describing relationships between categorical variables; correlation describes relationships between continuous variables.
2. Neither association nor correlation implies causation. These terms describe only the relationship and strength of this relationship.
3. Correlation is a matter of "degree." It can range from −1.00 (inverse proportionality) to +1.00 (proportional relationship). Zero signifies no correlation.

Quick HIT

Selection Bias

Ideally, comparison groups should be identical in all respects other than factor under investigation. In reality, this comparison group does not exist due to confounding variables. Therefore, randomized controlled trials are preferred to minimize confounding.

H. Causality.

It is very difficult to prove causality. The following factors help assess causality, but none can give indisputable evidence of a cause-and-effect relationship:

1. Strength of association
2. Biologic plausibility—does the association make biologic sense?
3. Consistency of the association across different studies
4. Dose–response relationship
5. Experimental evidence to support causality—for example, if you eliminate an exposure, does this reduce the incidence of a particular disease?
6. Temporal sequence (very important)—the causative factor must precede the effect.
7. Experimental evidence—has a randomized controlled trial (highest level of evidence) been performed?

Quick HIT

The only inherent advantage of randomized controlled trials over observational studies is the reduction in confounding.

I. Bias

1. A study that is biased lacks internal validity. Bias can be introduced in the design of a study or during the statistical analysis because of the lack of statistical power (inadequate sample size). In addition, conflict of interest can introduce bias and affect the validity of a study. Critical appraisal of medical literature essentially requires the ability to identify bias.

2. There are multiple types of bias: selection bias, information bias, performance bias, detection bias, and attrition bias (see Clinical Pearl A-3).

CLINICAL PEARL A-3

Types of Bias

- **Selection bias—**occurs when there are differences in the characteristics of subjects between comparison groups of a study. Unequal distribution of confounding variables among the two groups leads to selection bias.
- **Information bias—**occurs during data collection, where collecting information about exposures and outcomes is subject to systematic distortion
- **Performance bias—**occurs when subjects in comparison groups are given different care (other than the intervention that is being studied). For example, only one group may receive counseling in addition to the intervention that is being studied (the counseling may affect the outcome in some way). Blinding is important in preventing performance bias (patient and investigators are not aware of the treatment rendered).
- **Detection bias—**refers to inconsistency in outcome assessment. Use of validated outcome measures and blinding of outcome assessors help prevent detection bias.
- **Attrition bias—**refers to patient drop-outs or exclusion from a study. There is no recognized drop-out rate that is deemed "acceptable." Drop-outs should be kept to a minimum, but if they do occur, **intent-to-treat analysis** is critical to maintain the integrity of randomization (see text).

3. A **confounding variable** is a factor other than the intervention under investigation that obscures the primary comparison.
   a. Common confounding variables include age, gender, comorbidities, smoking, and socioeconomic status.
   b. A true confounding variable must meet two criteria: It must be associated with the explanatory (independent) variable, **and** it should be a risk factor for the outcome of interest.
   c. Randomized controlled trials control for both known and **unknown** confounders.

Quick HIT

When evaluating a randomized clinical trial, go through this checklist to assess whether a study is biased:

- Proper randomization
- Concealment of allocation
- Blinding
- Completeness of follow-up and intent-to-treat analysis

4. Minimizing bias in randomized clinical trials hinges on the following:
   a. **Proper randomization—**each patient should have an **equal** chance of receiving either treatment.
   b. **Concealment of allocation—**the person enrolling patients into study should be unaware of next "assignment" into either the experimental or control group. This can be done with sealed opaque envelopes, remote allocation (call made to a separate department to determine patient allocation), or computerized allocation.
   c. **Blinding—**the higher the level of blinding, the lower the risk of bias. The following participants can potentially be blinded depending on the nature of the study: Patients, physicians, data collectors, assessors of outcome, data analysts. A study should describe precisely which participants were blinded. Terms such as "double" and "triple" blinding, if not defined, are confusing and should be avoided because textbooks and physicians often have varying interpretations of these terms.
   d. **Intent-to-treat analysis—**drop-outs are analyzed in groups to which they were initially assigned. Excluding drop-outs from analysis threatens the balance that randomization achieves. Drop-outs often do worse than patients who remain, and excluding them creates bias.

Quick HIT

Intent-to-Treat Analysis

Patients are analyzed with the group to which they were randomly assigned, regardless of whether they actually received that treatment or completed the study.

J. Glossary of Common Statistical Terms

1. Mean—the average
2. Median—value corresponding to the middle case or middle observation (i.e., 50% of values are less than and 50% of the values are more than the median)
3. Mode—value that occurs most often
4. Standard deviation (SD)—used for normal distributions. An SD of ± 1 includes about 68% of the observations, an SD of ± 2 includes about 95% of the observations, and an SD of ± 3 includes about 99.7% of the observations
5. Incidence—number of new cases of a disease per year
6. Prevalence—overall proportion of the population who have the disease
7. Relative risk—incidence in exposed group/incidence in unexposed group. Relative risk can be calculated only after a prospective or experimental study
8. Odds ratio—a method of estimating the relative risk in retrospective studies. It is the probability of an event happening divided by the probability of the event not happening
9. Reliability—ability of a test or measure to reproduce the same results under the same conditions
10. Validity—extent to which a study correctly represents the relationships being assessed
    a. Internal validity—a study that suffers from bias lacks internal validity
    b. External validity—a study may have internal validity but its results may not be generalized to a larger population (lacks external validity)

End-of-Life Issues and Informed Consent

1. Advance directives are written instructions given by patients that specify what actions to take for their health if they are not able to make decisions due to illness or incapacitation.
    a. A living will leaves instructions for treatment, outlining the patient's wishes. A living will may specify that patient does not want to be on

a ventilator, or does not want a blood transfusion. These instructions should be respected even if a family member disagrees with them.

   b. A power of attorney (healthcare proxy)—person appointed by patient to make decisions on their behalf.
   c. Bioethics committee input can be helpful when a patient has lost decision-making capacity and there is no advance directive. In most situations the next of kin becomes the patient's surrogate decision maker.
   d. Court order—when patient has no capacity to make a decision and the family is in disagreement and there is no healthcare proxy specified.
   e. State or public appointed guardian—when the patient lacks decision-making capacity and is unrepresented, for example, there is no next of kin available or family declines to participate in healthcare decision making.
2. An adult who can participate in the discussion regarding the risks and benefits of treatment decisions has ultimate decision-making capacity about their own medical care. Note that decision-making capacity is specific to the particular decision at hand (meaning, a patient may have capacity to make one decision but lack capacity to make another decision if unable to understand the benefits of treatment or risks of foregoing treatment). If such an adult demonstrates decision-making capacity and declines a treatment, respect the patient's autonomy, even if that treatment is clearly indicated or the standard of care. For example, you cannot compel a Jehovah's Witness to accept blood products. Patients can make an informed decision to decline medical care even if this results in their death or disability.
   a. All medical interventions (including artificial nutrition and hydration) may be stopped at the patient's request.
   b. If a patient who is mentally incapacitated is in a persistent vegetative state or comatose, family members (even if not formally appointed as proxy decision makers) can withdraw life-sustaining treatments based on prior conversations with the patient or their understanding of the patient's values.

Quick HIT

DNR (do not resuscitate)—refers only to withholding cardiopulmonary resuscitation during cardiac arrest.

3. Definition of death: An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all the functions of the entire brain, including the brain stem. To declare an individual dead, either the heart and lungs OR the brain and brain stem stop functioning permanently.
4. Informed consent.
   a. Every procedure needs informed consent. Only the person performing the procedure should obtain consent.
   b. Informed consent should include the following:
      - The diagnosis or medical problem for which the physician is recommending treatment.
      - A description of the proposed treatment or procedure, including its purpose, duration, methods, and implements used, as well as the probability of success.
      - All material risks of the procedure or treatment.
      - Any reasonable alternatives to the proposed procedure.
      - The risks of not being treated.
   c. For a patient who does not have capacity to consent (comatose, incapacitated)—a healthcare power of attorney can consent or decline. If there is uncertainty about a patient's capacity due to an underlying primary neurologic or psychiatric disorder, neuropsychiatric evaluation may be necessary. In general, any physician can determine capacity unless legal documentation is required for public guardianship (in which case evaluation by a psychiatrist is often necessary). If a patient is determined to be incapacitated and if there is no POA, the wishes of family (or next of kin) should be respected. If there is disagreement among family members, or concerns about whether the surrogate decision maker has the patient's best interests in mind, consult the hospital bioethics committee.

d. If an adult regains capacity, then the duty of informed consent returns to the patient and the healthcare POA cannot make decisions.
e. Emergencies: Consent is not needed in an emergency, it is implied in situations in which the benefits clearly outweigh risks of treatment. If a pediatric patient needs emergent life-saving treatment and parent is not available for consent, physician may proceed to treat patient without consent.
f. Remember that minors (under 18) cannot make decisions or consent to or decline medical treatments. Only parents or legal guardians can consent. Patients under 18 do not require parental consent in the following situations:
   - Court-ordered emancipation
   - Situational emancipation (married, raising children, members of the military service, living apart from parents and financially self-reliant, and other related situations)
   - STI treatment or HIV testing
   - Contraceptive care, prenatal care, or abortion (although the latter now varies state to state)
   - Substance use treatment or counseling
   - Mental health treatment

Questions

1. A 61-year-old male presents to your office with the chief concern of "coughing up blood and weakness" for the past 3 weeks. He reports several episodes every few days of coughing of bright red blood, approximately one to two tablespoons each time. The patient denies any chest pain, fevers, chills, or recent travel. He has mild dyspnea at baseline. He has recently developed lower extremity muscle cramps and has difficulty rising from a chair. Past medical history is significant for COPD diagnosed 5 years ago and HTN. He has a 40-pack-year smoking history and currently smokes 1 pack per day. Examination is notable for end-expiratory wheezing and a prolonged expiratory phase on lung auscultation. He has 3/5 hip flexion and decreased deep tendon reflexes bilaterally in lower extremities. Laboratory tests are normal including electrolytes. CXR reveals typical changes seen in COPD (flattened diaphragms, hyperinflation) and a perihilar mass. What is the most likely diagnosis?
   A. Bronchial carcinoid
   B. Adenocarcinoma
   C. Large cell carcinoma
   D. Squamous cell carcinoma
   E. Small cell carcinoma

2. A 67-year-old male presents to the ED with LLQ pain that began a few hours ago. His PMH is significant for hypertension, CHF, and nephrolithiasis. He reports one episode of blood in his stools a few months ago. Vital signs are as follows: Temperature 101.1°F, BP 130/76, HR 70. On physical examination, he has moderate tenderness to palpation in the LLQ but no epigastric tenderness or flank tenderness. His examination is otherwise unremarkable. A digital rectal examination shows normal stool. Urinalysis is unrevealing. Laboratory

tests reveal a leukocyte count of 16,000 cells/μL and normal electrolytes and renal function. What is the next step in managing this patient?

A. Check a serum lactate
B. Obtain a retroperitoneal ultrasound
C. Prepare the patient for colonoscopy
D. Obtain contrast-enhanced CT of the abdomen
E. Proceed to the operating room

3. A 64-year-old female with a history of HTN, CAD, and CHF presents to the ED with a chief concern of left-sided chest pain that began 4 to 5 hours ago. She has a history of periodic episodes of chest pain for which she takes sublingual nitroglycerin, but today's episode has been more severe, lasted longer, and is not relieved by nitroglycerin. She denies nausea, vomiting, any radiation of the pain, or diaphoresis. Temperature 97.8°F, BP 136/76, HR 105, RR 20. Physical examination includes clear lungs on auscultation, no JVP elevation, and no LE swelling. ECG shows Q waves in lateral leads and no ST elevation. Troponin is 0.50 ng/mL. Aspirin is given. What is the best next intervention at this time?

A. Alteplase
B. Heparin
C. Hydralazine
D. Furosemide
E. Digoxin

4. A 64-year-old male presents to the ED with symptoms of RUE weakness and slurred speech. His symptoms started 6 hours ago and have not improved. He has a medical history significant for hypertension and diabetes. Neurologic examination confirms RUE paresis and dysarthria. Rest of examination is normal. Vitals: BP 190/100 mm Hg, HR 75. Labs are notable for glucose of 135 mg/dL, A1c 7.3%. CT head shows an area of ischemia without associated hemorrhage. Home medications include metformin and lisinopril. What is the most important intervention at this point?

A. Insulin
B. Heparin
C. Aspirin
D. Alteplase
E. Labetalol

5. A 58-year-old male presents to your office with weakness in his legs and a history of frequent falls over the past few months. He also complains of fatigue at the end of the day. He denies any back pain. He does not drink alcohol or smoke. His medical history is significant for gastric carcinoma for which he underwent total gastrectomy 2 years ago and there are no signs of recurrence. On physical examination, he is found to have conjunctival pallor, increased deep tendon reflexes, and mild weakness of his lower extremities, along with diminished vibratory sense in his toes. Cerebellar testing is normal. His examination is otherwise unremarkable. What would be the best test in confirming the cause of his symptoms?
   A. Serum folate level
   B. CBC with mean corpuscular volume
   C. Intrinsic factor Ab
   D. MRI lumbar spine
   E. Methylmalonic acid level

6. A 37-year-old nulliparous female presents to your office with chronic progressive weakness. Her symptoms have developed gradually over the past year and she has largely ignored them. She reports a recent weight gain of 25 lb over the past year and has been feeling melancholy for the past few months. She has also had back pain for the past several months. Her medical history is significant for mild HTN and diabetes on insulin, both of which she was diagnosed with over the past year. Physical examination reveals mild obesity, with fat deposition mainly around the trunk and the posterior neck. You note some facial hair and scattered purple striae on the abdomen. Radiographs reveal a compressed fracture at the level of T11. Vital

signs are as follows: BP 140/85 mm Hg, HR 70. What would be the most appropriate next test in this patient?

A. Serum ACTH
B. MRI brain
C. CT abdomen
D. 24-hour urine-free cortisol
E. CRH stimulation test

7. A 56-year-old male with a history of cigarette smoking and hyperlipidemia is brought to the ED with severe, crushing chest pain that has lasted for 90 minutes. He states that he felt ill all day and then started experiencing pain in his jaw, which progressed to chest pain with radiation to the right arm associated with nausea. Vital signs are as follows: Temperature 97.4°F, HR 50, BP 85/45 mm Hg, RR 22, pulse oximetry 98% on room air. Examination reveals JVP without elevation, normal lung examination, and no peripheral edema. An ECG reveals significant ST elevations in leads II, III, and aVF. What is the next best step in managing this patient?

A. Nitroglycerin
B. Intravenous fluids
C. Furosemide
D. Metoprolol
E. Morphine

8. A 45-year-old female with history of type 2 diabetes, alcohol use disorder, and COPD is evaluated for confusion in the ED. She lives with a roommate who states the patient was acting differently from baseline. The patient is agitated, not oriented, and not responding to questions appropriately. Vitals T 37.5°C, HR 110, RR 30. Physical examination reveals lungs with minimal end-expiratory wheezing. Physical examination is otherwise normal. UA is within normal limits. Labs: Na 140 mEq/L, Cl 105 mEq/L, K 5 mEq/L, HCO_3 15 mEq/L, BUN 20 mg/dL, Cr 1 mg/dL, glucose 100 mg/dL. ABG: pH 7.30, PCO_2 25 mm Hg, PO_2 85 mm Hg. What is the next appropriate medical intervention?

A. Fomepizole
B. Acetylcysteine
C. Albuterol
D. Sodium bicarbonate
E. Insulin

9. A 54-year-old male presents to your office for a physical examination. His PMH is significant for HTN, for which he takes amlodipine. He has never had screening for colorectal cancer previously. On examination, there are no palpable masses in the abdomen, no tenderness, and bowel sounds are normal. He denies any change in bowel habits. The remainder of his physical examination is unremarkable. He is given a fecal immunochemical test (FIT) for screening, which returns positive. What is the appropriate next step in managing this patient?
   A. Flexible sigmoidoscopy
   B. Digital rectal examination
   C. Video capsule endoscopy
   D. CT colonography
   E. Colonoscopy

10. A 55-year-old male presents to the ED with epigastric abdominal pain. He does not have nausea, vomiting, or diarrhea. His PMH is significant for stroke, HTN, and osteoarthritis of his knees. Medications include a daily baby aspirin, enalapril, and ibuprofen. Vital signs are as follows: RR 20, BP 155/90 mm Hg, HR 70. His physical examination reveals epigastric tenderness, no abdominal distention, and rectal examination notes dark stool in the rectal vault. Laboratory tests reveal hemoglobin of 10.2 g/dL, platelets 190 × 10^3/μL. Hepatic panel is normal. Na 135 mEq/L, K 4.5 mEq/L, Cl 105 mEq/L, HCO_3 22 mEq/L, BUN 45 mg/dL, Cr 1.2 mg/dL. INR is normal. What is the next recommended step in managing this patient?
    A. IV omeprazole
    B. IV octreotide
    C. Platelet transfusion

D. RBC transfusion
E. IV fluids

11. A 45-year-old female is admitted to the hospital with abdominal swelling. She has not previously sought medical care and had been well until 3 months ago when swelling began. Swelling gradually began and has worsened to the point that she is now short of breath and has difficulty mobilizing. She was born in Mexico but has been living in the United States for the past 20 years. She does not take any medications. She does not drink alcohol. Lung examination reveals decreased breath sounds at the bases. Cardiac examination reveals no murmurs and JVP is flat. Her abdomen is moderately distended with a positive fluid wave; her liver is not palpable. Skin examination is normal. She has asymmetric lower extremity edema with a tender right calf. Labs reveal elevated cholesterol levels. A diagnostic and therapeutic paracentesis is performed, which reveals the following: serum albumin 2.5 g/dL, serum total protein 5.0 g/dL, ascites total protein 2.3 g/dL, ascites albumin 1.6 g/dL. What test is the most likely to reveal the cause of her ascites?
A. Echocardiogram
B. Pelvic ultrasound
C. Liver biopsy
D. Ascitic fluid adenosine deaminase
E. 24-hour urine protein

12. A 65-year-old man presents to the ED with lower extremity weakness. His symptoms started 1 week prior when he noticed difficulty walking. He now has difficulty raising his legs off the floor and is using a wheelchair. He does not have any pain in his lower extremities but describes paresthesias in his legs. He does not have weakness elsewhere, dyspnea, or any other associated symptoms. Prior to this he had an episode of nonbloody diarrhea a few weeks ago that self-resolved. His only past medical history is hypertension for which he takes hydrochlorothiazide. Cardiac examination is normal. Pulmonary examination reveals nonlabored breathing, clear lung fields, and O_2

saturation 98% on room air. Neurologic examination reveals normal speech without dysarthria and no cranial nerve deficits. Strength is 5/5 in bilateral upper extremities in shoulder/elbow/wrist flexion and extension, 1/5 bilateral ankle dorsiflexion/plantar flexion, 1/5 knee flexion/extension, 2/5 hip flexion. Achilles and patellar reflexes are absent bilaterally. Sensory examination is normal. Labs including electrolytes, renal function, and blood counts are normal. CT head is unrevealing for stroke or other acute findings. Lumbar puncture is performed and analysis reveals 3 WBC/mm^3, protein 100 mg/dL (normal range <50 mg/dL), Gram stain negative. What is the most appropriate therapy?

A. Prednisone
B. IVIG
C. Ciprofloxacin
D. Pyridostigmine
E. Botulism antitoxin

13. A 24-year-old female presents to your office for a routine examination. She reports a history of heavy menstrual bleeding since menarche. Her mother had similar symptoms. On further questioning, she states that she has episodes of epistaxis about once every 2 weeks and has a tendency to bruise easily. Her physical examination is unremarkable. CBC results are as follows: Hgb 7.9 g/dL, MCV 69 fL. Platelet count is 230,000/μL. PT 12 seconds (normal), and PTT 30 seconds (normal). A hepatic panel including bilirubin is normal. What is the most appropriate test to order?

A. Fibrinogen
B. Direct antiglobulin test (Coombs test)
C. Factor IX level
D. Mixing study
E. Ristocetin cofactor activity

14. A 43-year-old male presents to the ED with a headache. His headache developed acutely over the past few hours and is severe in nature. His pain is located at the top of his head. He denies any associated

weakness. He does not have double vision, dizziness, nausea, vomiting, or phono/photophobia. He has no prior history of headaches. His vitals are as follows: BP 144/90 mm Hg, T 37.2°C. Examination reveals a middle-aged man in moderate distress. Neurologic examination is negative for focal weakness or sensory deficit. No nuchal rigidity is noted. Cranial nerves are intact. CT brain without contrast is obtained and negative for ischemia or hemorrhage. What is the next most appropriate intervention?

A. Sumatriptan
B. MRI brain
C. Cerebral angiogram
D. CT brain with contrast
E. Lumbar puncture

15. A 59-year-old female presents to the office because she is "sick and tired" of this cough she has had for 5 years, and it is getting worse. The cough is often productive of watery mucus. She is also becoming increasingly short of breath and cannot climb a flight of stairs without taking a rest. She does not have chest pain, paroxysmal nocturnal dyspnea, fevers, chills, or weight loss. PMH is significant for HTN and a 35-pack-year history of cigarette smoking. Vital signs are as follows: Temperature = 99.0°F, HR 75, RR 21, BP 158/82 mm Hg. O_2 saturation is 94% at rest and reaches a nadir of 90% with activity. Physical examination reveals an obese woman in no acute distress. On lung auscultation, there are coarse breath sounds bilaterally but no wheezes or crackles. Chest radiograph is significant for prominent lung markings at the bases. PFTs show FEV_1/FVC ratio 0.60 and FEV_1 65%. What is the most effective long-term intervention for this woman?

A. Smoking cessation
B. Tiotropium inhaler
C. Salmeterol inhaler
D. Oxygen therapy
E. Azithromycin

16. A 56-year-old male comes to your clinic requesting advice after recent cardiac surgery. The patient had a long-standing murmur and was diagnosed with mitral stenosis. He eventually underwent repair with a prosthetic valve and his symptoms of dyspnea have resolved. He has resumed physical activity and seeks to maintain his current health. He wants advice on future procedures and possible risk of infection. Which procedure warrants antibiotic prophylaxis to prevent endocarditis?

- **A.** Colonoscopy
- **B.** Wisdom tooth extraction
- **C.** EGD
- **D.** Bronchoscopy without biopsy
- **E.** Dilatation ureteral stricture

17. A 67-year-old male presents to clinic with right hip pain for the last week. He has no history of falls or injury. The pain came on suddenly as he was getting up from a chair. PMH is significant for HTN and hypothyroidism. He started using a cane a few days ago but due to increasing pain is now in a wheelchair. On physical examination, he has severe pain with any attempted motion of the right hip joint. Pulses are palpable bilaterally, and neurologic examination is normal. Radiographs of the right hip are obtained and show normal bone density with a displaced fracture of the right femoral neck. Labs: Na^+ 135 mEq/L, Cl 105 mEq/L, HCO_3 25 mEq/L, $Ca2^+$ 11.0 mg/dL, Cr 1.9 mg/dL, Hgb 9.5 g/dL, MCV 90 fL. Labs a year ago were completely normal. He is up-to-date on routine health screening. In addition to referring him for hospital admission for orthopedic repair of the fracture, what other testing is indicated to best explain the patient's findings?

- **A.** SPEP
- **B.** ^{99m}Tc bone scan
- **C.** PTHrP
- **D.** PTH
- **E.** DEXA

18. A 38-year-old female presents to clinic with chief concern of fatigue and weight gain for the past 5 to 6 months. Her fatigue has affected her performance as a surgeon, and she has been having difficulty concentrating during operations. She recently began losing hair. She feels more tired than usual and has difficulty playing with her dogs in the evening. She did not have any of these symptoms until 6 months ago. She denies heat/cold intolerance. She has gained 10 lb in the past 6 months despite attempting to eat well and exercise a few times weekly. She is generally happy and has not had recent mood changes. She does not smoke and drinks alcohol socially. She has an IUD. HR 50, BP 120/80 mm Hg, RR 16, BMI 31. Physical examination reveals a normal pharynx, no neck fullness, and no palpable thyroid nodules. Abdomen is soft, nontender. Skin examination reveals no lesions/rashes and no lower extremity edema. She has an appropriate mood and affect. She donated blood last week and was told that her Hgb was normal. What is the appropriate next step in managing this patient?

- **A.** US thyroid
- **B.** TPO
- **C.** Thyroid uptake scan
- **D.** FNA
- **E.** TSH

19. A 38-year-old female presents to the ED with a 2-day history of shortness of breath. She states that she has felt tired for the past couple of weeks but is not able to describe any other symptoms. She has never smoked. PMH is unremarkable. On physical examination, she has diffuse wheezing but no calf tenderness or lower extremity edema. Her vitals are as follows: temperature 98.6°F, BP 126/74 mm Hg, pulse 80, RR 20. D-dimer is elevated. CXR reveals no consolidation. She subsequently undergoes a CT scan which reveals a 6-mm round nodule without associated lymphadenopathy or effusions and no evidence of pulmonary embolism. There are no calcifications in the nodule. She is treated with albuterol and discharged home in stable condition. What is

the appropriate recommendation to this patient upon outpatient follow-up with her primary care physician?

A. Follow-up CT chest
B. Bronchoscopy
C. Needle biopsy
D. Follow-up CXR
E. PET-CT scan

20. A 75-year-old female with a history of two prior MIs presents to the ED after a syncopal episode. She reports fatigue and dyspnea for 2 months. She has mild chest pain and dyspnea. A 12-lead ECG reveals a bradycardia with a ventricular rate of 35 bpm. BP 80/55 mm Hg. On physical examination, she is in mild distress. Her heart sounds are regular, bradycardic, with no murmurs. Lungs are clear. Her skin is cold and clammy. Home medications include ASA, atorvastatin, carvedilol, empagliflozin, eplerenone, and sacubitril-valsartan. ECG is as below (Figure 1). Prior echocardiogram from 6 months prior showed EF of 29% with diastolic dysfunction; valves were normal without stenosis or regurgitation. Laboratory testing reveals normal electrolytes including Mg and K. Troponin is elevated. What is the most appropriate immediate management?

A. Echocardiogram
B. Nitroglycerin
C. Metoprolol
D. Atropine
E. ICD

21. A 40-year-old male presents to your office with “chest burning” and cough for the past 5 to 6 months. The pain is intermittent and not related to meals. Triggers for his symptoms include drinking alcohol and lying flat in bed. He does not have dysphagia or odynophagia. He has tried over-the-counter calcium carbonate and famotidine as needed with minimal relief of symptoms. He has not had recent weight loss, dark, or bloody stools. He is a nonsmoker. He does not have history of seasonal allergies, itchy/watery eyes, sneezing, dyspnea, or prior diagnosis of asthma. His PMH is significant for HTN, which is controlled with amlodipine. He does not take any other medications. Physical examination is unremarkable. How would you treat this patient?

- **A.** Helicobacter pylori antigen
- **B.** EGD
- **C.** pH monitoring
- **D.** Gastrin level
- **E.** Trial of omeprazole

22. A 32-year-old female presents to your office with a history of diarrhea and intermittent abdominal cramping/bloating with flatus. She reports having loose, watery diarrhea very frequently on and off for several years, but her symptoms have been worse recently. Prior to initial onset she had normal, formed daily bowel movements. Her weight is 75 kg and on review of her records she has lost 7 kg since her symptoms started. She has not had blood in the stool. There is no family history of IBD or colon cancer. The patient’s only past medical history is depression for which she is undergoing cognitive-behavioral therapy. Laboratory evaluation reveals AST 65 U/L, ALT 55 U/L, TSH 3.0 mU/L, and Cr 1.0 mg/dL. Blood counts show Hgb 9.8 g/dL with MCV 70 fL. Vitals: T 37°C, BP 120/85 mm Hg, RR 16. Physical examination reveals a rash on extensor surfaces of both elbows with erythematous vesicles present. She is a college student and is studying for her midterm examination. What test should be the next intervention?

- **A.** EGD with small bowel biopsy

B. Colonoscopy
C. Loperamide
D. Sertraline
E. Skin biopsy

23. A 65-year-old female with a history of type 2 diabetes, HTN, and a large anterior wall MI 5 years ago presents to the clinic with subacute progressive dyspnea. At baseline the patient finds it difficult to do any household chores. She has dyspnea at rest and is homebound because of her symptoms. Vital signs are: Temperature 98.7°F, HR 62, RR 19, BP 160/85 mm Hg, oxygen saturation 90% on room air. There are bibasilar crackles with scattered expiratory wheezes. There is 2+ pitting edema of the lower extremities. JVP is measured just above the clavicle. An ECG reveals left ventricular hypertrophy (LVH), with Q waves and T-wave inversions in V_1 to V_4 and diffuse nonspecific ST segment abnormalities. A CXR shows cardiomegaly and congestion of the pulmonary vasculature. Prior echocardiogram from 1 year ago shows EF 30% with anterior wall motion abnormalities. Labs are normal including CBC, Cr, K. The patient's medications include empagliflozin, losartan, carvedilol, and aspirin. What is the most important long-term intervention for this patient?

A. Isosorbide dinitrate
B. Spironolactone
C. Hydralazine
D. Digoxin
E. Furosemide

24. A 23-year-old female is in your clinic to be evaluated for wheezing and shortness of breath. She has no history of respiratory problems prior to the past few months. She recently joined a gym and began increasing her physical activity. Every time she runs she has similar symptoms of wheezing and shortness of breath. Symptoms seem to last the duration of the activity but will resolve afterward. She has no dyspnea between episodes. She does not have fevers, chills, runny nose, sneezing, sputum production, or congestion. She has no known

allergies. She does not smoke. Physical examination reveals a young woman with no respiratory distress. Cardiac examination reveals normal rate, no murmurs are appreciated, and JVP is not elevated. Lung examination reveals normal expansion, good air movement in all lung fields without rhonchi or wheezing. Peak flow in clinic is normal. PFTs are obtained and show FEV_1/FVC 0.8. FEV_1 is 93% of predicted. TLC is normal. What is the most appropriate management?

A. CXR
B. Inhaled fluticasone
C. Reassurance
D. Inhaled albuterol PRN
E. Inhaled salmeterol

25. A 35-year-old female undergoes routine laboratory workup for an insurance physical. Labs reveal WBC 5.0 $10^3/mm^3$, Hgb 12.7 g/dL, Cr 1.0 mg/dL. Urinalysis shows 2+ bacteria and urine culture grows 10^5 CFU *Escherichia coli.* PMH is otherwise negative. She has had occasional UTIs in the past but none for the past year. Her only medication is an oral contraceptive. Urine hCG is negative. Vital signs are: Temperature 98.6°F, BP 115/60 mm Hg, pulse 80, RR 20. Lungs are clear to auscultation bilaterally. Heart rate and rhythm are regular, without murmurs. The patient appears well and is alert and oriented. She has no tenderness at the costovertebral angles and no suprapubic tenderness. What is the appropriate next step in managing this patient?

A. Nitrofurantoin
B. Cephalexin
C. Trimethoprim-sulfamethoxazole
D. No treatment
E. Repeat urinalysis and culture

26. A 45-year-old female is brought to the ED complaining of fatigue. The patient has been feeling extremely weak over the past few days. Today she stood up and almost fainted, prompting her visit. She has had cough, rhinorrhea, and nasal congestion for the past week. Today she also began having nausea, vomiting, and severe abdominal pain. Past

medical history is significant for hypertension, CKD, and SLE. Home medications are lisinopril, hydroxychloroquine, and prednisone 20 mg daily. Vitals: Temperature 38.5°C, BP 85/55 mm Hg, HR 126. In general, she appears weak and lethargic. Her heart sounds are tachycardic, regular, without murmurs. Her lungs have occasional rhonchi but no wheezing. Her abdomen is diffusely tender throughout without rebound tenderness. Labs: Na 124 mEq/L, K 5.3 mEq/L, Cr 3.0 mg/dL (baseline 1.8). Hgb is 11.1 g/dL. The patient is diagnosed with Influenza A and started on IV fluids. After 2 L of crystalloid fluids her blood pressure is 90/60 mm Hg. What is the most appropriate next step?

- **A.** Cortisol level
- **B.** IV hydrocortisone
- **C.** CT adrenal glands
- **D.** MRI pituitary
- **E.** Cosyntropin stimulation test

27. A 71-year-old female presents to the ED with a 2-day history of severe abdominal pain. Pain developed suddenly with no clear correlation to meals. Her symptoms were mild at first, becoming severe in the next 6 to 10 hours. She has nausea, but no vomiting or dysphagia. Her past medical history is significant for GERD, HFpEF, type 2 DM, and atrial fibrillation. She is afebrile. HR 70, BP 135/85 mm Hg. Cardiac examination reveals a 3/6 systolic murmur in L axilla and irregularly irregular heart rate. Her abdominal examination reveals mild tenderness in the mid-abdomen. Her stool is dark. Laboratory studies show Hgb 10.0 g/dL, WBC 17.5 $10^3/mm^3$, Na 144 mEq/L, Cl 105 mEq/L, K 4.0 mEq/L, HCO_3 20 mEq/L, Cr 1.1 mg/dL, A1c 12.6%, and INR 1.4. Medications are metoprolol, apixaban, insulin, and enalapril, but she has difficulty with medication adherence. What is the appropriate next step in evaluation?

- **A.** CT angiography
- **B.** Gastric emptying study
- **C.** Colonoscopy
- **D.** EGD

E. Andexanet alfa

28. A 43-year-old male presents to your office with a 3-day history of chest pain, which is centrally located and radiates to the right side of his neck. The pain worsens with deep breathing and improves when he sits up. He has no nausea, vomiting, sweating, or SOB. He had an upper respiratory infection about 2 weeks ago, which resolved without treatment. PMH is significant for hyperlipidemia. He takes rosuvastatin. He smokes half a pack of cigarettes a day. Vital signs are: temperature 99.4°F, BP 125/80 mm Hg, pulse 84. Physical examination is significant for a friction rub over the left sternal border heard best when he leans forward. A 12-lead ECG shows diffuse ST elevation in leads I, II, III, aVL, and V_2 through V_6. Echocardiogram shows an EF 50% with no regional wall motion abnormalities and normal valvular function. There is a small pericardial effusion. What is the most appropriate next step?

A. Coronary angiogram
B. Drainage of pericardial effusion
C. Prednisone
D. Azathioprine
E. Ibuprofen

29. A 55-year-old male with past history of COPD presents to the emergency department with chest pain and SOB that started last evening. His chest pain is right-sided and is stabbing in quality, and the pain worsens with inspiration. He is short of breath even at rest. He does not recall any traumatic event or overexertion. He does not have fevers, chills, or sputum production. He has a 35-pack-year smoking history. He takes tiotropium and albuterol PRN. Temperature 98.2°F, BP 130/80 mm Hg, HR 115, RR 24. Pulse oximetry shows 84% oxygen saturation on room air. He is 6 ft 2 in and 175 lb, and he otherwise appears healthy. Physical examination reveals absent breath sounds in the right upper lung field. There is minimal end-expiratory wheezing in both lungs without crackles. No stridor is noted. Heart examination reveals regular tachycardia without murmurs. JVP is flat.

There is no lower extremity edema. What is the appropriate next step in managing this patient?

A. Albuterol–ipratropium nebulizer
B. Prednisone
C. Chest tube insertion
D. Azithromycin
E. Pleurodesis

30. A 78-year-old male with a history of aortic stenosis with a mechanical aortic valve, hypertension, and type 2 diabetes presents to office for evaluation. He is doing well, except for some palpitations over the past few months. He does not have associated shortness of breath, syncope, or a history of falls. On physical examination, you note an irregularly irregular heart rhythm and a mechanical S2. Examination is otherwise normal. You obtain an ECG, which confirms the irregularly irregular arrhythmia. The patient has no history of bleeding and Hgb is normal. What is the recommended medication for prevention of thromboembolic events?

A. Aspirin
B. Clopidogrel
C. Apixaban
D. Warfarin
E. Dabigatran

31. A 73-year-old male with HTN presents to the office with a 3-month history of chest pain and dyspnea induced by lifting weights, shoveling snow, and running on a treadmill. Vital signs are as follows: Temperature 98.3°F, HR 85, RR 17, BP 165/85 mm Hg. Physical examination reveals a 4/6 crescendo–decrescendo murmur heard at the right upper sternal border with radiation to the carotid arteries, weak and delayed carotid pulses, and an S4 gallop. ECG reveals sinus rhythm without arrhythmia. Echocardiogram reveals EF 45% and aortic valve area 0.8 cm^2. Prior coronary angiography 1 year prior showed 20% lesion in the mid left anterior descending artery, 30% right coronary artery lesion, and no significant stenosis in the left

circumflex artery. What is the most effective intervention strategy for this patient?

A. Nitroglycerin
B. Aortic valve replacement
C. Aspirin
D. Carotid Doppler
E. Coronary artery bypass grafting

32. A 38-year-old female presents to clinic with left knee pain for the past 2 to 3 months. She reports no history of injury. PMH is significant for SLE and CKD. She has recently been running more in an attempt to lose weight but her pain is now limiting her activity. She describes her pain as primarily "around and under my knee cap." She points to her patella and the anterior aspect of her knee as the site of her pain. She especially has difficulty climbing and descending stairs. She has full range of motion without pain. She has no tenderness along medial or lateral joint lines. Examination reveals negative anterior and posterior drawer tests, full ROM in flexion and extension without crepitus, no effusion or erythema present. X-rays of the knee reveal normal alignment with preservation of joint space. Labs: Na 135 mEq/L, K 4.0 mEq/L, Cr 2.3 mg/dL. ANA is positive. ESR 10 mm/hr. What is appropriate next step in the management of this patient?

A. Corticosteroid injection
B. Physical therapy
C. Knee arthroscopy
D. MRI knee
E. Ibuprofen

33. A 57-year-old male had a fasting plasma glucose level of 160 mg/dL 1 month ago. Today, his fasting glucose level is 140 mg/dL. His medical history is significant for HFpEF and hyperlipidemia. His current medications include aspirin, lisinopril, and metoprolol. He is 5 ft 11 in and weighs 215 lb. BP 142/79. This patient is asymptomatic, and his physical examination is unremarkable. Labs: Na 142 mEq/L, K 4.0 mEq/L, Cr 1.7 mg/dL. Urine albumin: Cr ratio is 100 mg/g. A1c is

7.1%. In addition to lifestyle changes including increase in physical activity, diet changes, and weight loss, how would you manage this patient?

A. Hydrochlorothiazide
B. Insulin
C. Amlodipine
D. Hydralazine
E. Lisinopril

34. A 36-year-old female presents to your office with a 4-month history of dry cough, SOB, and fatigue. She has a 10-pack-year smoking history. Vital signs: Temperature 98.2°F, BP 132/79 mm Hg, HR 74, RR 16. Pulse oximetry shows 96% O_2 saturation on room air. Examination reveals crackles bilaterally in the lower lung fields. There is no wheezing. She has two tender erythematous nodules on her left leg measuring approximately 3 × 3 cm. CXR shows bilateral hilar adenopathy. What is the next best test in order to confirm the suspected underlying diagnosis that explains the patient's constellation of symptoms?

A. Serum calcium
B. CT chest
C. Serum ACE level
D. Biopsy of leg lesion
E. Bronchoscopy and biopsy of hilar lymph node

35. A 68-year-old male with a history of lung cancer undergoes follow-up labs after recent cycle of chemotherapy. He has mild difficulty with concentration over the past week but is otherwise able to complete all of his daily tasks. He reports no nausea, vomiting, or positional lightheadedness. He has no other significant past medical history. He takes no medications. Vital signs are as follows: Temperature 99.8°F, RR 18, BP 135/88 mm Hg, pulse 76. On examination, he is alert and oriented. Cardiac examination reveals regular rate and rhythm, no murmurs, JVP not elevated. Lung and abdominal examinations are normal. There is no lower extremity edema. Skin turgor is normal.

Neurologic examination reveals 5/5 strength in all extremities, no focal deficits, and normal gait. Laboratory tests reveal the following: serum Na^+ 121 mEq/L, K^+ 4.3 mEq/L, BUN 7.0 mg/dL, Cr 0.4 mg/dL, glucose 106 mg/dL. TSH 2.0 mU/L. Serum osmolality 250 mOsm/kg, urine Na 45 mEq/L, urine osmolality 450 mOsm/kg. What is the most appropriate management of this patient?

A. Administer IV normal (0.9%) saline
B. Initiate fluid restriction
C. Initiate hemodialysis
D. Administer hypertonic (3%) saline
E. Administer hydrochlorothiazide

36. A 20-year-old male presents for evaluation after an episode of dark urine. He felt well up until 2 weeks ago when he had a sore throat and mild fever for which he did not seek medical care. Urinary symptoms started the day prior to evaluation. He does not have cough, dyspnea, hemoptysis, joint pains, dysuria, or flank pain. He had two recent sexual partners but uses condoms consistently. He has no prior medical history or family history of renal diseases. BP 145/90 mm Hg, HR 65, T 37°C. Physical examination reveals a well-appearing male with normal heart sounds, clear lungs, and mild lower extremity edema. There are no skin lesions. Urinalysis is dark red in color. Microscopic examination is positive for deformed RBCs and RBC casts. Cr is 1.6 mg/dL. What is the most likely test to help aid in the diagnosis of this patient?

A. ANCA
B. Anti-GBM
C. HIV
D. Antistreptolysin titer
E. IgA levels

37. A 31-year-old female with hypertension presents to your office with painful joints for the past 4 months affecting her wrists, ankles, and knees. She also reports several outbreaks of a rash over her face over the past few months. Her only medications are hydrochlorothiazide

and acetaminophen as needed. Vital signs are as follows: Temperature 99.2°F, RR 20, BP 145/83 mm Hg, pulse 78. Physical examination reveals three ulcers in her mouth and mild swelling of the left wrist and ankle. She has 1+ pitting edema in her lower extremities bilaterally. Examination is otherwise unremarkable. Labs reveal a WBC count of 2,300/mm^3, Hgb 12.2 g/dL, and platelets 82,000/mm^3. What is the most likely diagnosis?

- **A.** Osteoarthritis
- **B.** Reactive arthritis
- **C.** Behçet disease
- **D.** Gout
- **E.** SLE

38. A 62-year-old male presents to your office accompanied by his husband. He notes a tremor in his hands that disappears when he writes or handles utensils. His husband thinks he stares often and does not show as much emotion as before. He still participates in his usual activities and enjoys gardening with his husband. His appetite and sleep habits have remained unchanged. Weight is similar to his last clinic visit. His husband notices that he moves slower than before and walks steadily. On examination, you note a mild resting tremor and a fixed expression on his face. There is resistance on passive range of motion with upper extremities. Gait is slow, without imbalance or falling, and his arms do not swing when walking. He scored 26/30 on Mini-Mental Status Examination. What is the best intervention to improve the patient's symptoms?

- **A.** Fluoxetine
- **B.** Carbidopa–levodopa
- **C.** Propranolol
- **D.** Memantine
- **E.** Deep brain stimulation

39. A 24-year-old male presents to clinic with worsening right lower quadrant cramping abdominal pain for 2 months. He reports having diarrhea on and off for the past 1 to 2 years. He had a colonoscopy

with a terminal ileum biopsy showing ulceration, acute inflammation, and noncaseating granulomas. Two months ago, he was placed on mesalamine. He has lost 20 lb since then despite attempting to increase his dietary intake. He has no other medical problems and takes no other medications. His physical examination reveals mild tenderness in the RLQ with normal bowel sounds. There are no anal fissures or fistulae. His stool appears normal on rectal examination. Vital signs are as follows: Temperature 98.7°F, RR 15, BP 122/78 mm Hg, pulse 65. BMI 21. Labs show normal liver and renal function. CBC shows WBC $10.1 \times 10^3/mm^3$, Hgb 9.9 g/dL, and MCV 82 fL. CT abdomen reveals thickened mucosa in distal ileum with adjacent mesenteric stranding; there is no obstruction, fistula, abscess, or free air present. What is the next best step in treatment?

A. Loperamide
B. Azathioprine
C. Infliximab
D. Surgical resection
E. Ciprofloxacin and metronidazole

40. A 58-year-old male presents to your office with left wrist pain for the past 3 months. He cannot recall any history of injury or trauma. He works as a car mechanic. He also has a new granddaughter who is 6 months old that he babysits every weekend. He is an amateur golfer when time allows. He does not have neck pain. He has no associated paresthesias or weakness. PMH is significant for mild HTN and chronic kidney disease with a baseline Cr of 2.5 mg/dL. Examination reveals normal sensation throughout bilateral upper extremities. Neck flexion/extension/rotation does not reproduce his symptoms. Strength testing is normal in bilateral upper extremities. There is no evidence of muscle wasting on examination of the hands. With the patient making a fist surrounding the thumb, ulnar deviation of the wrist produces pain over the distal radial styloid. Prolonged wrist flexion does not elicit pain. Palpation over the flexor surface of the wrist base does not reproduce the patient’s symptoms. Pain is not elicited with resisted

wrist extension or flexion. What is the most appropriate next step in management?

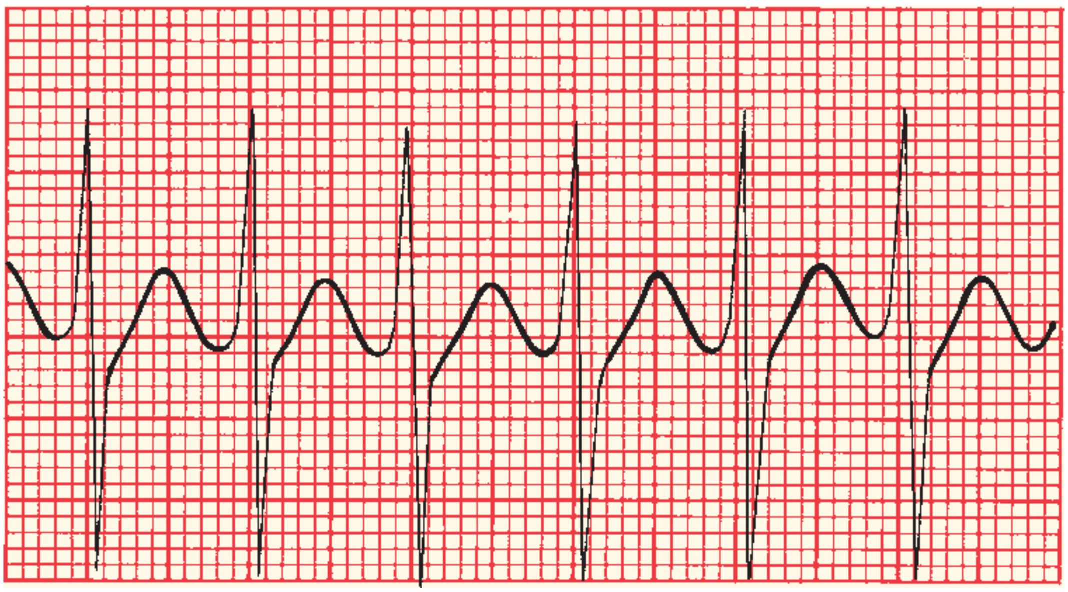
A. Thumb spica splint
B. Wrist splint
C. Counterforce forearm brace
D. Carpal tunnel corticosteroid injection
E. Ibuprofen

41. While on-call in the hospital, you are called to evaluate a 74-year-old female for SOB and increasing oxygen requirements. She does not have a cough. The patient was admitted yesterday with multiple leg fractures after a motor vehicle accident. She has been on strict bed rest since admission while a plan is made for surgical repair. She has mild chest pain and feels short of breath. Past medical history is significant for HFpEF and COPD. She is adherent with her medications, which include tiotropium, furosemide, and carvedilol. Temperature 100.0°F, BP 116/74 mm Hg, pulse 120, RR 24, oxygen saturation 91% on 4 L of oxygen via nasal cannula. General examination reveals a patient who is alert and oriented to name and year but not to place. Mental status on admission was normal and she has no history of neurocognitive disorder. Lung examination reveals good air movement throughout with no wheezing, crackles, or consolidation. JVP is not elevated. There are scattered petechiae on the upper chest. Bilateral lower extremities have symmetric 1+ edema without calf tenderness. CT chest shows scattered ground-glass opacities without consolidation, no segmental or subsegmental emboli, and no effusions. What is the appropriate next step in management?

A. Albuterol
B. Reduction of fracture
C. Furosemide
D. Levofloxacin
E. IV heparin

42. A 38-year-old man is evaluated for palpitations in the ED. He has had these symptoms several times over the past year but this episode is

worse. He does not report any associated chest pain, lightheadedness, or syncope. He has no known history of medical problems and takes no medications. Examination reveals an adult male in no significant distress. He is normotensive. Cardiac examination is significant for regular tachycardia with no JVP elevation. Lungs are clear without crackles or wheezing. There is no lower extremity edema. ECG is shown (Figure 2). What is the best intervention at this point?



A. Valsalva maneuver
B. Adenosine
C. Metoprolol
D. Digoxin
E. Cardioversion

43. A 38-year-old female presents to clinic with pain in her wrists, ankles, and knees bilaterally. She reports noticing numbness and morning stiffness in her hands about 1 year ago, mostly in cold weather. This stiffness gradually spread to her wrists, knees, and ankles, with lesser involvement of her shoulders. The stiffness and pain are worse in the morning but improve as the day wears on. Symptoms have gradually worsened. Some days she cannot go outside her house because of the pain. She has no history of rash or photosensitivity. She often feels

tired and "worn out." Medical history is significant for HTN, for which she takes hydrochlorothiazide. On examination, her metacarpal joints and wrists are swollen and tender, as are her knees and ankles bilaterally. Her examination is otherwise unremarkable. Labs reveal normal liver and renal function. CBC is unremarkable. ESR 65 mm/hr. CCP is positive. ANA is negative. X-rays of hands show erosive changes in MCP joints. What is the most important intervention for this patient to control her disease?

A. Prednisone
B. Corticosteroid injection
C. Indomethacin
D. Methotrexate
E. Physical therapy

44. A 60-year-old female presents to the ED with right upper quadrant abdominal pain that began several hours ago. She has had occasional RUQ pain over the past 3 months but never this severe. Her PMH is significant for HTN and osteoarthritis. On physical examination, she appears ill. Scleral icterus is present. She has RUQ abdominal tenderness without peritoneal signs. There are no surgical scars on the abdomen. Initial vital signs are as follows: Temperature 102.1°F, RR 16, BP 95/70 mm Hg, pulse 120. Laboratory tests reveal ALT 136 U/L and AST 119 U/L, ALP 105 U/L, direct bilirubin 4.5 mg/dL, and WBC count $16.8 \times 10^3/mm^3$. Ultrasound of the abdomen shows common bile duct dilatation with obstructing gallstones. Piperacillin-tazobactam is started and the patient is resuscitated with IV fluids. Repeat vitals after antibiotics and 4 L of IV fluids are administered show a BP 110/82 mm Hg, HR 85, and temperature 98.8°F. Repeat hepatic labs show increasingly elevated transaminases and hyperbilirubinemia. What is the next step in managing this patient?

A. Cholecystectomy
B. Liver biopsy
C. ERCP
D. MRCP
E. Percutaneous transhepatic cholangiography

45. A 42-year-old healthy female presents to clinic for pre-employment screening. She is starting a new job as a bus driver and needs to have a physical and TB test before being hired. She reports no fever, chills, sputum, or weight loss. She was born in the United States and has not traveled outside of the country. She has never received a tuberculosis vaccine. She has not had known contact with anyone infected with tuberculosis. She has never used IV drugs. Recent STI screening, including HIV, was negative. Physical examination is normal. PPD testing is performed and on reevaluation after 48 hours, there is 10 mm of induration. What is the best recommendation to the patient?

A. AFB sputum culture

B. Rifampin, isoniazid, pyrazinamide, ethambutol

C. Rifampin

D. Chest x-ray

E. No further intervention

46. A 34-year-old male presents to clinic with left knee pain swelling. He has occasional pain in both knees that is usually dull and resolves with acetaminophen. Over the past few days, he has had swelling which has made it difficult to move the joint. He had a similar episode of swelling a year ago that resolved on its own but this episode is much more severe. He does not recall preceding trauma and does not report morning stiffness. On physical examination, he has a moderate left knee effusion with overlying erythema. He has crepitus in both knees. Strength is normal, and examination does not indicate any ligamentous instability. X-ray shows mild narrowing of the joint space and calcification of the cartilage. Aspiration of the effusion reveals straw-colored fluid, 25,000 WBCs, 85% PMNs, Gram stain and culture are negative. Evaluation for crystals reveals no intracellular negatively birefringent crystals, but does reveal multiple intracellular positively birefringent rhomboid-shaped crystals. What is the most appropriate laboratory test to obtain?

A. Uric acid

B. PTH

C. ANA

D. ESR
E. HLA-B27

47. A 62-year-old female presents to your clinic with questions regarding her new diagnosis of osteoporosis. She had a hip fracture 6 months ago after a fall. Subsequently, she had a prolonged hospital course complicated by a provoked DVT for which she completed therapy with apixaban. She has had no further falls and is back to her baseline level of activity after a 1-month rehabilitation stay. She had a DEXA scan which showed a T-score of −2.6 in the hip and −2.3 in vertebrae. Her past medical history includes achalasia for which she gets dilatations as needed. Currently she only takes omeprazole on a daily basis. Labs including renal function, calcium, and vitamin D are all normal. She is inquiring about further options to prevent her from having fractures. What is the appropriate management of this patient besides recommending continued supplementation with vitamin D and calcium?

A. Zoledronic acid
B. Alendronate
C. Raloxifene
D. Calcitonin
E. Estrogen

48. A 53-year-old female presents to the hospital with abdominal pain. She is diagnosed with cholecystitis and undergoes a cholecystectomy. The following day she complains of palpitations. On questioning she has had an irregular heart beat off/on for the past few months that acutely worsened during this episode. She also notes a 15-lb weight loss over the past month. She denies dizziness, syncope, dyspnea, or chest pain. She has a known history of hyperlipidemia but has otherwise been healthy. Medications include ASA and atorvastatin. Vitals: Temperature 102.4°F, BP 155/88 mm Hg, pulse 134, oxygen saturation at room air 96%. On physical examination, the patient is agitated and confused, answering questions inappropriately. Skin is diaphoretic. Neck is supple without tenderness and no palpable

nodules or enlargement. Cardiac examination reveals an irregular rhythm, tachycardia, and no murmurs. ECG confirms atrial fibrillation with rapid ventricular response. TSH is <0.01 mU/L. What is the most appropriate next step in the management of this patient?

- **A.** Radioactive iodine uptake scan
- **B.** Iodine
- **C.** US thyroid
- **D.** Propranolol
- **E.** Thyroidectomy

49. A 61-year-old male who has been your patient for several years presents to clinic with two episodes of bloody urine over the past 24 hours. He denies any flank pain, dysuria, fevers, or chills. His urine stream is strong, he is able to void completely and does not experience the need to start/stop or strain during urination. PMH is significant for hyperlipidemia, HTN, type 2 diabetes, glaucoma, and osteoarthritis. He has smoked one pack of cigarettes per day for the past 35 to 40 years. Physical examination reveals no costovertebral angle or suprapubic tenderness. Prostate examination reveals a nontender, nonenlarged prostate. Urinalysis shows gross hematuria without proteinuria, pyuria, or RBC casts. Cr 1.1 mg/dL. Urine culture is negative. What is the appropriate next step in managing this patient?

- **A.** CT urography
- **B.** Ultrasound kidneys and bladder
- **C.** Renal biopsy
- **D.** PSA
- **E.** Prostate biopsy

50. A 57-year-old male presents to your office with a 2-week history of cough. The cough is associated with clear sputum, occurs daily and has persisted over the past 2 weeks. He has occasional dyspnea and frequent wheezing. He does not have myalgias, fevers, chills, sore throat, rhinorrhea, congestion, headache, or loss of taste or smell. He has experienced chest discomfort due to excessive coughing. PMH is unremarkable and he does not take any medications. Temperature is

99.1°F, RR 18, O_2 saturation is 96% on room air. On examination, the patient is in no respiratory distress and is breathing comfortably. Auscultation of lungs reveals diffuse expiratory wheezing but no crackles or rhonchi. CXR shows normal expansion of the lungs without infiltrates or effusions. A rapid SARS-CoV-2 PCR is negative. Peak flow is 530 L/min (expected 556 L/min). What is the most appropriate management?

A. Prednisone
B. Oseltamivir
C. Azithromycin
D. Albuterol
E. Sputum culture

51. A 32-year-old male, who recently moved to the area, presents to clinic for the first time for a routine checkup. PMH is significant for type 2 diabetes. He is 5 ft 9 in and weighs 215 lb. The only medication he takes is metformin. He smokes half a pack of cigarettes a day; does not drink alcohol; and exercises sporadically, approximately once every 2 weeks. His mother died at the age of 62 years due to an MI. His father is 73 years of age and is healthy. Physical examination is normal. Vital signs are: BP 146/95, pulse 73, RR 19, temperature 98.2°F. Which of the following lifestyle modifications has been shown to result in the greatest reduction in blood pressure?

A. Dietary Approaches to Stop Hypertension (DASH) diet
B. Weight loss
C. Decreasing alcohol consumption
D. Increasing exercise
E. Smoking cessation

52. The patient in the previous question returns to clinic in 6 weeks for a repeat evaluation. He has no concerns. He states that he has been walking briskly for 30 minutes four times a week, has lost 10 lb, and has been eating a healthier diet. His laboratory results are within normal limits. Hemoglobin A1c is 7.2%. CXR, ECG, and urinalysis are normal. His BP today is between 140/90 and 145/95. Physical

examination is unchanged from 2 months ago. What is your recommended treatment?

A. Lisinopril
B. Amlodipine
C. Hydrochlorothiazide
D. Atenolol
E. Propranolol

53. A 17-year-old female is referred to the ED by her primary physician; she presents with a 3-day history of fevers, dysuria, and vomiting. She has not had vaginal discharge, abdominal pain, or diarrhea. She is sexually active with her partner. Vital signs are as follows: Temperature 103°F, RR 20, BP 98/65, pulse 100. She appears ill and is unable to tolerate liquids, but she is alert and oriented. Her examination is positive for suprapubic as well as costovertebral angle tenderness bilaterally. Urinalysis reveals numerous WBCs and bacteria, and it is positive for WBC casts and leukocyte esterase. Other laboratory study results are within normal limits, including a negative urine pregnancy test. What is the likely diagnosis?

A. Pyelonephritis
B. Nephrolithiasis
C. Appendicitis
D. Ectopic pregnancy
E. Acute interstitial nephritis

54. A 32-year-old male presents to the ED with severe low back pain for the last 5 weeks. He reports that the pain is most severe when he first wakes up in the morning and gradually improves with exercise throughout the day. He cannot recall any trauma or insult to his back when the pain started. He does not have any pain or numbness in the lower extremities. Bowel and bladder function is normal. Physical examination reveals a moderately overweight male in some distress. He has very minimal tenderness on palpation of his low back. Neurologic examination is normal. What is the appropriate next step in managing this patient?

A. Local heat
B. Ice pack
C. Nonsteroidal anti-inflammatory drugs (NSAIDs)
D. Epidural steroid injection
E. Surgical laminectomy

55. A 29-year-old male with a history of asthma presents to the ED with severe SOB for the past 2 days. He also complains of sore throat, generalized malaise, and a nonproductive cough. He denies chest pain, fever, and chills. Temperature 98.9°F, HR 95, RR 33, BP 140/82, and O_2 saturation 90% on room air. Breathing is labored, and he is speaking in short gasps. Lung auscultation reveals bilateral diffuse expiratory wheezing. There is no urticaria or angioedema on skin examination. ABG is drawn: pH 7.42, $PaCO_2$ 43 mm Hg, PaO_2 70 mm Hg, bicarbonate 22 mEq/L. What is the appropriate next step in managing this patient?

A. Intubation
B. IV ceftriaxone and azithromycin
C. Subcutaneous epinephrine for bronchodilation
D. Nebulized ipratropium for bronchodilation
E. Nebulized albuterol for bronchodilation

56. A 22-year-old female presents to the ED with abrupt onset of a rash, high fever, and vomiting. Vital signs are as follows: Temperature 104°F, HR 118, RR 22, BP 76/40, and pulse oximetry 98% on room air. On examination, she appears confused and disoriented. Her skin is warm, and there is a diffuse macular rash over her body. She is admitted to the ICU and subsequently develops multisystem organ dysfunction. Which of the following organisms is most likely implicated in this patient's diagnosis?

A. *Escherichia coli*
B. *Neisseria meningitidis*
C. *Staphylococcus aureus*
D. *Streptococcus pneumoniae*

E. *Rickettsia rickettsii*

57. A 33-year-old male comes to the clinic with a 4-day history of chest pain. The pain radiates to the right side of the neck and is worsened by deep inspiration and improved by leaning forward. Several weeks ago, he had a fever and cough, which have both since improved. He is afebrile, BP is 130/85, and pulse is 88. On examination, there is a scratching sound heard over the left sternal border on expiration. ECG shows ST elevation in leads I, II, III, avL, and V_2 to V_6. The patient is offered treatment but declines all medications. Which of the following is the most common complication if this disease remains untreated?

A. Cardiac tamponade
B. Recurrent pericarditis
C. Constrictive pericarditis
D. Ventricular free wall rupture
E. Valvular insufficiency

58. A 52-year-old woman with a history of type 2 diabetes mellitus and hypertension presents to the emergency department with fevers, chills, and abdominal pain. The symptoms began about 1 week ago and have been getting worse. The abdominal pain is associated with nausea and vomiting, and she has not been able to eat. On examination, her temperature is 102.1, blood pressure is 104/68 mm Hg, heart rate is 94/min, and respiratory rate is 16/min. Her abdominal examination shows right-sided pain to deep palpation, and she has severe right-sided costovertebral angle tenderness. Laboratories demonstrate a leukocytosis (15,400/mm^3) and urinalysis shows WBCs, WBC casts, protein, and bacteria. Despite IV ceftriaxone for 5 days, the patient remains febrile. The patient's urine culture is positive for *Escherichia coli* and is sensitive to ceftriaxone and ciprofloxacin. What is the appropriate next step in management?

A. Renal biopsy
B. CT scan with contrast
C. Continue the current antibiotic
D. Stop ceftriaxone and start ciprofloxacin

E. Stop ceftriaxone and repeat urine culture

59. You are paged to evaluate a 33-year-old female with SOB and tachycardia. She normally takes inhaled fluticasone and albuterol for asthma, however she is not currently responding to the albuterol. On examination, she appears anxious and is moderately short of breath. There are soft bilateral wheezes on examination with quiescent breath sounds, with a prolonged inspiratory and expiratory phase and use of accessory muscles of respiration. Temperature is 99.4°F, pulse 116, BP 116/56, RR 36, oxygen saturation is 91% on room air. Examination shows use of accessory muscles on inspiration. An arterial blood gas is obtained and shows a pH of 7.4, PCO_2 of 40 mm Hg, and a PO_2 of 60 mm Hg. What is the appropriate next step in the management of this patient?

A. Increase supplemental oxygen flow rate
B. IV corticosteroids
C. Azithromycin
D. Intubation
E. Nebulized albuterol

60. A 61-year-old man with a history of chronic alcohol use disorder and parathyroid adenoma presents with pain in his left knee for the last 2 days. He reports no fevers, chills, night sweats, or history of trauma to the knee, but does note abdominal pain and constipation. Physical examination is significant for tenderness and erythematous skin overlying the left knee. There is also marked swelling of the left knee. Laboratory findings reveal an elevated calcium level (12.1 mg/dL). If joint aspiration is performed, which of the following will be seen on synovial fluid analysis?

A. Negatively birefringent needle-shaped crystals
B. Positively birefringent rhomboid-shaped crystals
C. Neutrophil predominance with gram-positive cocci
D. Negatively birefringent needle-shaped crystals AND gram-positive cocci
E. Normal synovial fluid findings

61. A 26-year-old man presents to his primary care physician with fatigue, headache, and a sore throat for the past week. There is also nausea and diarrhea, but no weight loss, productive cough, or difficulty breathing. He has no known past medical history, does not take any medications, and has no recent sick contacts. He is sexually active and uses condoms inconsistently; he drinks alcohol heavily on the weekends and has had previous IV drug use. On examination, his temperature is 39°C and the rest of his vital signs are normal. He has nontender cervical and axillary lymphadenopathy, tonsillar exudates, and mild splenomegaly. There are also several painful, well-demarcated ulcers within his mouth and a mild maculopapular rash over his chest and arms. A rapid Strep test and a monospot (heterophile antibody) test are negative; further screening for chlamydia, gonorrhea, syphilis, and HIV antibody is negative. What is the likely diagnosis?

- **A.** Hodgkin lymphoma
- **B.** Acute retroviral syndrome
- **C.** Infectious mononucleosis
- **D.** Secondary syphilis
- **E.** Upper respiratory infection

62. A 30-year-old medical student is undergoing medical screening in order to start a rotation at a new hospital. She has no current symptoms and reports no previous medical problems. She is originally from South Africa and her vaccinations are up-to-date, including a BCG vaccine she received as a child. A purified protein derivative (PPD) is placed and read 48 hours later, which shows an area of induration that is 11 mm wide. What is the most appropriate next step in management?

- **A.** Start rifampin, isoniazid, pyrazinamide, and ethambutol
- **B.** Obtain a chest x-ray; if normal, reassure the patient
- **C.** Obtain a chest x-ray; if normal, start rifampin, isoniazid, and pyridoxine for 3 months
- **D.** Start rifampin, isoniazid, and pyridoxine for 3 months
- **E.** Reassurance

63. A 35-year-old male presents with a 6-month history of fatigue and lethargy. His medical history is unremarkable. He has not had melena, recent trauma, or surgery. He reports that he does not drink alcohol, smoke, or take any medications. He appears well nourished. Vital signs are as follows: BP 130/80, pulse 70, RR 16. Laboratory test results are as follows: Hb 7.6 g/dL and MCV 68 fL. The remainder of his laboratory test results are normal. Which of the following is the best next step in management of this patient?

- **A.** Serum iron studies
- **B.** Hemoglobin electrophoresis
- **C.** Serum lead levels
- **D.** Coombs test
- **E.** Stool FIT test

64. A 56-year-old female presents to the ED with severe abdominal pain, primarily in the epigastric region. She has had two episodes of vomiting in the past 5 hours. She describes the pain as sharp, with occasional radiation to her back. PMH is significant for type 2 DM, HTN, alcohol use disorder, asthma, and chronic low back pain. Her current medications include metformin, insulin, amlodipine, albuterol inhaler, and oxycodone. She has had abdominal pain several times in the past year, but never this severe and never associated with vomiting. On examination, she has tenderness in the epigastric region. There is mild guarding but no rebound. Physical examination is otherwise unremarkable. Temperature is 101.3°F, BP 136/88, pulse 116. She is alert and oriented and in obvious distress. Which of the following is the most specific finding in this condition?

- **A.** Elevated amylase
- **B.** Elevated ALT
- **C.** Elevated lipase
- **D.** Positive fecal fat test
- **E.** Calcifications on x-ray

65. A 37-year-old female presents to your office with a history of fatigue for the past few months. She does not have any other concerns. After a

thorough medical history, she admits to mild constipation that is not troublesome for her. She reports a 5-lb weight gain over the past 6 months, which she attributes to living a more sedentary life of late due to her fatigue and lethargy. Her physical examination is unremarkable; her thyroid does not seem enlarged, although her face is slightly puffy. Which of the following is the best next step in management?

A. Free T4 levels
B. Thyroid-stimulating hormone (TSH) levels
C. Thyroglobulin levels
D. Radioactive iodine uptake (RAIU) scan
E. Biopsy

66. A 21-year-old male college student is brought to the ED by his friends after developing fever, neck stiffness, confusion, and severe sensitivity to light. His friends note that a few hours ago, he lost consciousness and was shaking for a few minutes. Vital signs on admission are as follows: Temperature 105°F, RR 20, BP 120/75, pulse 92, and pulse oximetry 99% on room air. Examination reveals a confused male patient with nuchal rigidity and a left-sided facial droop. His headache acutely worsens when you ask him to rotate his head quickly side to side. Which of the following is the next best step in management?

A. CT scan
B. MRI
C. Lumbar puncture
D. Administer dexamethasone
E. Administer empiric antiviral therapy

67. A 64-year-old male presents with back pain, constipation, and slight confusion for the past 5 to 6 months. Two days ago, he fell while shoveling snow, and he has pain in his right arm as well. Plain films of the spine show several small lytic lesions in the vertebral bodies at the L3 to L4 level. Right humerus films reveal lytic areas in the metaphysis and diaphysis of the right humerus with an associated nondisplaced fracture. Physical examination reveals tenderness on palpation of the low back and right humerus, but is otherwise

unremarkable. There is no splenomegaly or lymphadenopathy. CBC results are as follows: Hb 9.1 g/dL, MCV 90, platelet count 150,000/μL. Serum chemistries are as follows: Sodium 137 mEq/L, potassium 4.1 mEq/L, chloride 107 mEq/L, CO_2 24 mEq/L, glucose 89 mg/dL, BUN 46 mg/dL, Cr 3.5 mg/dL. ESR is 105 mm/hr. Which of the following additional findings do you expect with this patient's condition?

- **A.** Mechanical obstruction
- **B.** Electrolyte abnormality
- **C.** Hormone level abnormality
- **D.** Arterial blood gas abnormality
- **E.** Venous blood gas abnormality

68. A 47-year-old male presents to clinic with severe low back pain for the past 2 days. Over the past 2 days he has noted progressive weakness in his bilateral lower extremities. This morning he had an episode of urinary incontinence. His back pain is severe, sharp, and radiates down the right lower extremity. PMH is significant for asthma. He has had intermittent low back pain for the past 2 years but never this severe and never associated with weakness or urinary symptoms. On physical examination, he has very limited motion of his lumbar spine secondary to pain. He has 3/5 strength in gastrocnemius muscles bilaterally and 2/5 strength with great toe dorsiflexion bilaterally. He has diminished sensation throughout his lower extremities, and reflexes are diminished. Rectal tone is absent as is sensation in the perineal area. What is the next best step in management of this patient's condition?

- **A.** Physical therapy
- **B.** Surgery
- **C.** X-ray lumbar spine
- **D.** Bed rest
- **E.** NSAIDs

69. A 67-year-old female presents to the ED after a transient episode of visual loss in her right eye. She reports that she has had right-sided headache for several months, for which she takes ibuprofen, with some

relief. On physical examination, she has tenderness over her scalp in the left temporal region and complains that her jaw "gets tired with chewing." Neurologic examination is normal with no focal deficits. Vital signs are as follows: Temperature 101.1°F, HR 72, RR 16, BP 140/82. Which of the following is associated with this condition?

- **A.** Aortic aneurysm
- **B.** Inflammatory bowel disease
- **C.** Hepatitis B
- **D.** Smoking history
- **E.** Alcohol history

70. A 63-year-old female is brought to the ED by paramedics after an episode of syncope at home. Her husband witnessed the event. He states that she fell suddenly to the floor from a standing position. She lost consciousness for 5 seconds, after which she rapidly regained consciousness and was fully oriented. The patient remembers feeling lightheaded, nauseous, and developing "tunnel vision" prior to the event. No bowel or bladder incontinence was noted. PMH is significant for type 2 DM, HTN, and depression. She denies any chest pain or SOB. Vital signs are: Temperature 100.2°F, BP 118/68, pulse 84, RR 18. Oxygen saturation on room air is 96%. Physical examination is significant only for bruising of her left wrist and thigh. Heart and lung examination is normal. Which of the following is the most likely diagnosis?

- **A.** Arrhythmia
- **B.** Orthostatic hypotension
- **C.** Seizure
- **D.** Vasovagal syncope
- **E.** Aortic stenosis

71. A 63-year-old female presents to your office with mid to low back pain for the last year, which has worsened over the past 3 months. She does not report any weakness or radiating pain in her lower extremities. She currently takes oxycodone for her back pain with inadequate relief. She has difficulty sleeping at night because of the

back pain. PMH is significant for HTN, for which she takes a calcium channel blocker. Thoracic and lumbar spine radiographs show multiple compression fractures at T8, T11, L3, and L4, as well as diffuse osteopenia. Laboratory studies are as follows: WBC 8 ×10^3/mm^3, hemoglobin 9.7 g/dL, platelets 189 × 103/μL, Na+ 142 mEq/L, K− 4.1 mEq/L, BUN 43 mg/dL, creatinine 2.3 mg/dL, calcium 14.3 mg/dL. Physical examination reveals tenderness on palpation of thoracic and lumbar spine. She has limited lumbar flexion due to pain. Neurologic examination is normal. Which of the following would be most helpful to confirm diagnosis in this patient's condition?

- **A.** CA 15-3
- **B.** Carcinoembryonic antigen (CEA)
- **C.** Alkaline phosphatase
- **D.** Serum protein electrophoresis (SPEP)
- **E.** Bone scan

72. A 62-year-old female is brought to the ED by paramedics for confusion, headache, and vomiting over the past 12 hours. Vital signs are as follows: Temperature 96.9°F, HR 100, RR 22, BP 220/150. She is disoriented and uncooperative. Examination is otherwise unremarkable. What is the most likely diagnosis, and what is the most appropriate management?

- **A.** Hypertensive urgency (asymptomatic severe hypertension); gradual lowering of blood pressure with oral agents
- **B.** Hypertensive urgency (asymptomatic severe hypertension); rapid lowering of blood pressure with IV agents
- **C.** Hypertensive emergency; gradual lowering of blood pressure with oral agents
- **D.** Hypertensive emergency; rapid lowering of blood pressure with IV agents
- **E.** Hypertension; gradual lowering of blood pressure with oral agents

73. A 74-year-old male is brought to your office by his daughter, who is having increasing problems caring for him at home. She reports that he has recently had urinary incontinence and has been "clumsier" than

usual. She states that he behaves inappropriately at times, and on two occasions he has wandered outside the home and has gotten lost. He misplaces items frequently, and his personality has become more belligerent and demanding. He seems to lack judgment in social situations, and he never had this problem in the past. She states that these problems have become worse gradually over the past 4 months. On physical examination he has a wide-based gait with small steps. What is the most likely diagnosis?

A. Pseudotumor cerebri (idiopathic intracranial hypertension)
B. Alzheimer disease
C. Normal pressure hydrocephalus
D. Vascular dementia
E. Lewy body dementia

74. A 73-year-old female is brought to the ED by paramedics with SOB and progressive dyspnea. Her medical history is significant for an MI 5 years ago and chronic HFrEF. The patient has also had several episodes of ventricular tachycardia that ultimately required cardioversion. She is currently taking a prophylactic medication and has not had any recurrent arrhythmias. On physical examination, she is in moderate respiratory distress and she has dry rales throughout her lung fields. Temperature 99.1°F, BP 138/75, pulse 96, RR 28. CXR is normal, but CT scan of the chest shows diffuse reticular ground-glass opacities. Which of the following is contributing to this patient's symptoms and clinical findings?

A. Digoxin
B. Lisinopril
C. Amiodarone
D. Bleomycin
E. Losartan

75. A 39-year-old female presents to your office with a 3-year history of headaches. They occur once or twice per week, lasting several hours. The headaches are throbbing and are usually on her left side. During these episodes, the patient is incapacitated and must lie down in a dark

room for several hours. She is sensitive to light during the episodes and cannot move because of the pain. She is often nauseated and has vomited on several occasions. Medical history is significant for hypothyroidism, for which she takes levothyroxine. Her physical examination is unremarkable, but the patient endorses another similar headache and begins vomiting near the end of the examination. What is the appropriate next step in managing this patient?

A. Propranolol
B. Amitriptyline
C. Prochlorperazine
D. Verapamil
E. Sumatriptan

76. A 55-year-old female presents to your office for a routine follow-up examination. Medical history is significant for poorly controlled type 2 DM (20-year history), HTN, and osteoarthritis of bilateral knees. She also has had chronic renal insufficiency for the past 5 years. Her current medications include hydrochlorothiazide, lisinopril, metformin, insulin, and metoprolol. She has been taking increasing amounts of NSAIDs for the past several weeks for her painful knees. She is obese with 2+ peripheral pitting edema. She appears weak with dry mucous membranes and is tachycardic. Laboratory tests reveal the following: Na^+ 138 mEq/L, K^+ 4.6 mEq/L, Cl^- 104 mEq/L, HCO_3^- 27 mEq/L, Cr 3.6 mg/dL, WBC 7.9 $10^3/mm^3$, Hgb 8.2 g/dL, MCV 75 fL. On her last visit 3 months ago, her Cr was 2.3 mg/dL. Which of the following tests would be most helpful to determine the etiology of this patient's renal failure?

A. Urine dipstick
B. Urine sodium
C. Fractional excretion of sodium (FENa)
D. Renal ultrasound
E. Urine eosinophils

77. A 64-year-old female presents to the ED with sudden onset of severe chest pain that occasionally radiates to her back. She has a history of

angina and takes nitroglycerin, but this time the pain is much worse and is not relieved with nitroglycerin. PMH is significant for HTN. She is afebrile, HR 105, BP 160/105, RR 17. Cardiac enzymes are negative. CXR shows a widened mediastinum. What is the likely diagnosis?

A. Myocardial infarction
B. Aortic dissection
C. Stroke
D. Acute aortic regurgitation
E. Hypertensive emergency

78. A 17-year-old male presents to the ED with severe pain in his right leg and back that began suddenly a few days ago. The pain is sharp and throbbing. He has a history of sickle cell disease with frequent painful crises requiring hospitalization once or twice per year. He has no other medical problems. Vital signs are as follows: Temperature 101.6°F, HR 94, RR 20, BP 132/84. Oxygen saturation is 97% on room air. His right shin is very tender, as is his low back in the midline. His examination is otherwise unremarkable. CBC results are as follows: Hb 7 g/dL, MCV 94 fL. Osteomyelitis of the right tibia is ultimately diagnosed. What is the most likely cause of this patient's osteomyelitis?

A. Listeria
B. Salmonella
C. Shigella
D. Cryptosporidium
E. Campylobacter

79. A 42-year-old male presents to your office because he noticed a "lump" in his neck 1 month ago. He notes weight loss and palpitations, but has not had pain or dysphagia. On physical examination, you note a nontender, firm nodule about 2 cm in size to the left of the midline in the region of the thyroid gland. Vital signs are as follows: BP 125/82, pulse 75. He does not take any medications and has no significant medical history. He does not have any family history of thyroid disease

or cancer. His routine serum laboratory values (CBC and BMP) are normal. The physician decides to do a radioactive iodine uptake (RAIU) scan. Which of the following features is not associated with an increased risk of malignancy?

- **A.** Hard and immobile mass
- **B.** Cold nodule on RAIU
- **C.** Cervical lymphadenopathy
- **D.** Hot nodule on RAIU
- **E.** Microcalcifications

80. A 65-year-old female presents to your office with a 1-month history of intermittent neck and shoulder pain with SOB that normally occurs when she does chores around the house or climbs stairs. She is previously healthy and does not have any medical conditions. She does not smoke or drink alcohol. The patient is up-to-date on vaccinations and had a mammogram done at her previous appointment 1 year ago that was normal. BP 148/86 and pulse 88. She had a colonoscopy performed 6 years ago that was normal. You order an ECG, CXR, CBC, and electrolytes. What should be recommended to the patient at her visit today?

- **A.** Mammogram
- **B.** Colonoscopy
- **C.** Calcium and phosphorus levels
- **D.** Dual-energy x-ray absorptiometry (DEXA)
- **E.** CT scan of the chest

81. A 54-year-old male with a history of parathyroid adenoma presents to the ED with severe pain in his right knee. He says that the pain is extreme and intolerable, and he is in obvious distress. On examination, there is exquisite tenderness, erythema, and swelling of the right knee joint and it feels very warm to the touch. The pain began suddenly a few hours ago. He denies any previous episodes or pain in any other joints. He denies any trauma. Medical history is significant for osteoarthritis of his left knee, for which he takes ibuprofen. He drinks 6 to 7 glasses of wine per day. He does not take any other medications.

Vital signs are as follows: Temperature 100.5°F, RR 16, BP 140/85, pulse 78. Which of the following is the best next step in management for this patient?

- **A.** Indomethacin
- **B.** Joint aspiration with synovial fluid analysis
- **C.** Uric acid levels
- **D.** Knee x-ray

82. A 41-year-old male presents to your office with epigastric pain for the past several months. He takes over-the-counter antacids, but symptoms have been worse over the past month. He has not noted any weight loss, vomiting, hematemesis, or melena. The discomfort is worse after eating. Medical history is noncontributory. He takes no other medications. He smokes half a pack of cigarettes a day and drinks alcohol about once per week. Physical examination is unremarkable except for mild epigastric tenderness. A stool antigen *H. pylori* test is negative. What is the appropriate next step in managing this patient?

- **A.** Continue antacids
- **B.** Barium swallow evaluation
- **C.** Empiric 8-week trial with proton pump inhibitor (PPI)
- **D.** Upper GI endoscopy
- **E.** Observation

83. An 81-year-old female was in a motor vehicle accident 3 days ago and suffered a left femur fracture, for which she had surgery on the same day. She has been hospitalized since the day of surgery and has been taking part in daily physical therapy without difficulty. Her family (wife and daughter) report that she has not been "acting like herself" at times when they come to visit her. She becomes agitated and is belligerent toward them, and she sometimes wonders why she is in the hospital. She reports seeing "creatures." At other times, the patient is doing very well, and they do not notice these inconsistencies. The patient has a history of HTN. Current medications include a laxative and oxycodone for pain control. On examination, the patient is alert and oriented to time/place/person and is appropriately responding to

questions. She does not note any hallucinations. Neurologic examination is normal. Which of the following is true of this patient's condition?

A. Anticholinergic medications are first-line treatment
B. Pathologic findings include neurofibrillary tangles and β-amyloid plaques
C. Long-term memory is intact, but short-term memory is affected
D. This is an irreversible condition
E. Etiologies include infection and polypharmacy

84. A 49-year-old female presents to the ED with severe epigastric and RUQ abdominal pain that radiates to the right shoulder. Her symptoms started 3 days ago after she ate a hamburger but have progressively worsened over the past 12 hours. Her symptoms are worse with meals and she has vomited twice over the last day. She notes that over the past several months, a similar pain has intermittently occurred after eating that self-resolved each time. PMH is significant for type 2 diabetes, osteoarthritis, and HTN. Temperature 102.3°F, BP 146/80, pulse 110, RR 16. On physical examination, there is severe right upper quadrant pain on deep palpation, most pronounced on palpation after deep inspiration. Bowel sounds are diminished. The patient is lying on her side holding an emesis basin. Her labs are notable for leukocytosis and mildly elevated transaminases. Which of the following is causing this patient's disorder?

A. Alcoholic hepatitis
B. Gallstone obstruction in the cystic duct
C. Obstruction from carcinoma of the head of the pancreas
D. Gallstone obstruction in the common bile duct
E. Pancreatic inflammation

85. A 31-year-old female presents to your office with multiple musculoskeletal aches and pains including, but not limited to, her shoulders, elbows, knees, neck, and buttocks. She has had these symptoms for the past year. She does not sleep very well when the pain is severe and has no relief with NSAIDs. She has tried exercising

more, but the pain is persistent. On palpation, she has marked tenderness over both lateral epicondyles, the anterior aspect of her left shoulder, the medial aspect of her right knee, her posterior neck, and her left greater trochanter. There are no effusions at any of the above sites. Routine laboratory test results are normal. What is the appropriate next step in managing this patient?

- **A.** Prednisone
- **B.** Naproxen
- **C.** Amitriptyline
- **D.** Colchicine
- **E.** Steroid injections

86. A 52-year-old male with a long-standing history of alcohol use disorder is brought to the ED by his wife for vomiting blood. He vomited bright red blood at least twice this morning. PMH is significant for cirrhosis, HTN, and arthritis. He has never vomited blood before. On examination, the patient is awake but appears nervous and is in moderate distress. Delayed capillary refill is present. You are able to determine that he has vomited approximately 2 L of blood over the past 6 hours. Vital signs are: Temperature 99.2°F, BP 90/58, HR 134, RR 20. Pulse oximetry shows 98% oxygenation on room air. What is the appropriate immediate next step in managing this patient?

- **A.** Immediate upper GI endoscopy
- **B.** Administration of fluids
- **C.** Intravenous octreotide
- **D.** Intravenous (IV) proton pump inhibitor
- **E.** Reassurance

87. A 57-year-old female presents to the ED with acute on chronic abdominal pain and vomiting. The pain is diffuse and poorly localized. She has had these symptoms for the past month and has been constipated during this time. Over the last 3 days, her pain has worsened significantly. She has not had a bowel movement or passed gas in 3 days. She has a history of prior appendectomy. Vital signs are:

Temperature 99.2°F, BP 128/78, HR 78, RR 16. On physical examination, there is abdominal distention and no guarding or rebound tenderness. The remainder of the examination is normal. What is the next appropriate diagnostic step for this patient?

A. Abdominal ultrasound
B. Colonoscopy
C. Barium enema
D. Sigmoidoscopy
E. CT scan of abdomen and pelvis

88. A 43-year-old female with a history of Crohn disease presents to the ED with a 4-hour history of left flank pain radiating to her left groin. The pain was sudden in onset but was mild at first. However, it has been increasing in severity over the past 2 to 3 hours. The pain is now constant and excruciating. It was associated with nausea and vomiting, but the patient has not had fevers/chills. She has not seen any gross blood in her urine. Vital signs are as follows: Temperature 98.1°F, BP 148/88, pulse 93, RR 24. On physical examination, the patient is in obvious distress, writhing in pain. She has marked tenderness along the left flank, but the examination is otherwise unremarkable. Urinalysis reveals 2+ blood. Urine sediment reveals no casts but many RBCs and few WBCs per HPF. Laboratory tests reveal the following: WBC 8.2 $10^3/mm^3$, Hgb 11.9 g/dL, BUN 14 mg/dL, Cr 0.9 mg/dL. A urine pregnancy test is negative. What is the most likely diagnosis?

A. Pyelonephritis
B. Nephrolithiasis
C. Appendicitis
D. Ectopic pregnancy
E. Pancreatitis

89. A 39-year-old male is brought to the ED by his partner with the chief concern of acute SOB and anxiety that started suddenly 2 hours ago while he was working around the house. Last night he drank seven glasses of wine with his partner. He has not had chest pain. His PMH is unremarkable, however he uses diuretics to help “prevent bloating.”

Vital signs are: Temperature 99.1°F, BP 148/90, pulse 100, RR 34. Oxygen saturation is 94% on room air. On examination, the patient appears healthy although in moderate respiratory distress. Examination is otherwise unremarkable. Laboratory tests reveal: WBC 7.1 $10^3/mm^3$, Hgb 12.2 g/dL, $Na+$ 138 mEq/L, $K+$ 4.7 mEq/L, $Cl-$ 109 mEq/L, HCO_3- 25 mEq/L, BUN 14 mg/dL, Cr 0.9 mg/dL, glucose 106 mg/dL. ABGs are obtained and reveal: pH 7.52, HCO_3- 20 mEq/L, $PaCO_2$ 26 mmHg, PaO_2 70 mmHg. CXR and ECG are normal. Which of the following is the etiology of his acid–base disturbance?

- **A.** Accumulation of unmeasured anions due to hepatic metabolism of alcohol
- **B.** Vomiting due to alcohol toxicity
- **C.** Hyperventilation secondary to anxiety
- **D.** Electrolyte imbalance due to diuretic use
- **E.** Hypoventilation from respiratory depression due to alcohol intoxication

90. A 63-year-old male is brought to the ED by his wife for altered mental status. The patient regularly drinks alcohol and has a long-standing history of alcohol use disorder. Over the past 24 hours, he has become more confused and is not "acting like himself" according to his wife. She states that he has never acted like this before. On further questioning, the patient had an episode of massive hematemesis last year that required admission to the hospital, necessitating blood transfusion and other treatment that the wife does not recall. On physical examination, the patient is arousable and is alert to person but not to place or time. He is cachectic, with prominent veins over his abdomen. He has a significant ascites. There are several dilated superficial arterioles scattered throughout his body. When the patient extends his arms out in front of him, a jerking movement of the limbs is observed. Which of the following is the most appropriate next step in management?

- **A.** Furosemide
- **B.** Thiamine
- **C.** Lactulose

D. Morphine
E. Hydromorphone

91. A 65-year-old female presents to your office with a chief concern of low back pain and bilateral knee pain that is worse with activity and relieved by rest. She has had this pain for 6 or 7 months. She cannot recall any recent trauma or event precipitating the pain. One year ago, she suffered a distal radius fracture when she tripped in her bedroom and landed on her outstretched left arm. Medical history is significant for HTN, for which she takes hydrochlorothiazide. She smokes approximately 12 cigarettes per day and has a 25-pack-year history of smoking. She does not use alcohol. She does not exercise. On physical examination, she is obese, has no radicular symptoms, and the straight-leg test is negative. What is the appropriate next step in managing this patient?
A. Intra-articular corticosteroid injection
B. Acetaminophen
C. Naproxen
D. Allopurinol
E. Observation

92. A 46-year-old male presents to your office with fatigue for the past 2 months. He does not drink alcohol. His medical history is significant for HTN, for which he takes amlodipine. He has not had melena, hematochezia, or any other blood loss. His family history is noncontributory. He has no symptoms other than fatigue. He admits he does not have a good diet. Vital signs are: BP 135/85, pulse 70. Physical examination is unremarkable except for mild pallor. Digital rectal examination is unremarkable. Laboratory test results are: Hb 9.2 g/dL, MCV 117 fL. ECG is normal. The patient is started on folic acid and 4 weeks later presents with a hemoglobin level of 10.1 g/dL. However, he reports a new “pins and needles” sensation in his distal toes and fingers. Which of the following is the underlying cause of the patient’s current symptoms?
A. Inadequate treatment with folic acid

B. Iron deficiency
C. Glucose intolerance
D. Vitamin B_{12} deficiency
E. Peripheral neuropathy from diabetes mellitus

93. A 41-year-old female with history of hypertension presents to your office for a routine checkup. She is new to your office as she recently moved and presents to establish care. She takes blood pressure medications but cannot recall the names. On today's visit, her BP is 142/96. She is asymptomatic except for leg swelling. Physical examination reveals bilateral edema of the lower extremities. She smokes one pack of cigarettes per day and has a 20-pack-year history. Family history is negative. Her total serum cholesterol concentration is 175 mg/dL and HDL is 40 mg/dL. Routine laboratory test results are within normal limits. Which medication is most likely responsible for the patient's issue?

A. Amlodipine
B. Metoprolol
C. Hydrochlorothiazide
D. Metformin
E. Glipizide

94. A 73-year-old male is brought to the ED in a coma. He was delivered to the ED from a nursing home and was reported by the nursing home staff to have had a seizure that lasted less than 1 minute. He was subsequently confused and soon thereafter entered a comatose state. His medical history is significant for type 2 DM requiring insulin, HTN, and HFpEF. In the ED, the patient is very lethargic and responds only to pain stimuli. His vital signs are stable, and CBC and electrolyte levels are normal. Serum glucose is 16 mg/dL and serum insulin is elevated. C-peptide is 0.2 ng/mL (normal range, 0.5 to 3 ng/mL). Urine sulfonylurea level is undetectable. What is the likely cause of this patient's condition?

A. Factitious hypoglycemia from surreptitious injection of insulin
B. Insulinoma

C. Somatization disorder
D. Glucagonoma
E. Dehydration

95. A 78-year-old female presents to your office for a routine checkup. Her only concern is burning when she urinates that she has had for several weeks. Her medical history is significant for HTN and type 2 DM. She has four children, all delivered vaginally. Medications include lisinopril, insulin, metformin, and empagliflozin. She wears adult pads because she loses large volumes of urine throughout the day and usually cannot reach the bathroom in time. Physical examination is unremarkable. Vital signs are unremarkable. Routine laboratory test results are within normal limits except for a random blood glucose level of 210 mg/dL. Urinalysis shows positive nitrites and bacteria. She receives oral antibiotics for a urinary tract infection. After completing the course of antibiotics, she goes on a run, and feels a "pop" above her heel that is associated with severe pain. She has pain and difficulty with plantar flexion of the affected foot. Which of the following antibiotics is most likely responsible?
A. Trimethoprim-sulfamethoxazole
B. Metronidazole
C. Tobramycin
D. Ciprofloxacin
E. Azithromycin

96. A 33-year-old female presents to your office with insomnia and difficulty concentrating at work for several weeks. She reports a 20-lb weight loss over the past 2 to 3 months, despite eating more. When questioned, she reports that she frequently feels "hot and sweaty" at work and at home. She denies chest pain or palpitations but does have diarrhea frequently. Vital signs are: Temperature 98.9°F, BP 130/80, pulse 98, RR 15. She appears worried. On physical examination, she has warm and moist skin. She has a slight hand tremor. On palpation of her thyroid, you note a diffusely enlarged thyroid gland that is

nontender. Which of the following is the best next step in management?

- **A.** Free T4 levels
- **B.** Thyroid-stimulating hormone (TSH) levels
- **C.** Thyroglobulin levels
- **D.** Radioactive iodine uptake (RAIU) scan
- **E.** A fine-needle aspiration (FNA) biopsy

97. A 26-year-old medical student is injured via needle stick while drawing blood from a patient with chronic hepatitis B. The patient received her final hepatitis B vaccination of the series 7 years ago. The patient had her titers checked before clinical rotations 6 months ago and was found to be positive for anti-hepatitis B surface antibodies (HBsAbs). Which of the following is the best next step in the management of this patient?

- **A.** Hepatitis B immunoglobulin (HBIG) now
- **B.** Serologic testing for HBsAg
- **C.** Hepatitis B vaccination
- **D.** Reassurance

98. A 71-year-old female is brought to the ED by her husband for increased confusion over the past 3 days. The husband reports that the patient fell 4 days ago and immediately after the fall she was asymptomatic but over the ensuing days has become lethargic and more confused. PMH is significant for hyperlipidemia. She underwent a right total hip replacement 5 weeks ago and was diagnosed with a DVT 2 weeks after the operation. Medications include apixaban and atorvastatin. On examination, patient has slurred speech and appears confused. She is oriented to person but not to place or time. Neurologic examination is normal. The remainder of physical examination is normal. A head CT is ordered which confirms the diagnosis. Which of the following is the etiology of this patient's condition?

- **A.** Tearing of the middle meningeal artery
- **B.** Tearing of the bridging veins

C. Ruptured aneurysm
D. Hypertensive hemorrhage
E. Alzheimer disease

99. A 66-year-old male is brought to your office by his wife with productive cough, fever, and chills for the past 2 days. The patient lives with his wife and is retired. PMH is significant for type 2 DM, for which he takes metformin and insulin; HFrEF, with an ejection fraction of 40%; and a history of chronic kidney disease. He is alert and oriented. There is no history of smoking or alcohol use. On physical examination, the patient is lethargic. He has crackles over the left lower lung. Cardiovascular examination is normal. His JVP is flat and his extremities are warm. Vital signs are: Temperature 103.3°F, BP 82/54, HR 128, RR 24. Oxygen saturation on room air is 97%. CXR shows a consolidation in the left lower lobe of the lung. Laboratory test results show WBC 15 $10^3/mm^3$, hemoglobin 12 g/dL, Na 142 mEq/L, glucose 167 mg/dL, BUN 36 mg/dL, creatinine 1.5 mg/dL. Lactate is elevated. What is the likely diagnosis in this patient?
A. Cardiogenic shock
B. Pulmonary embolism
C. Sepsis
D. Severe sepsis
E. Septic shock

100. You are on-call in the hospital and called to see a 69-year-old male with acute dyspnea. Vital signs are: Temperature 100.1°F, BP 166/88, pulse 130, RR 33. On your arrival, the patient's oxygen saturation is 79% on a 100% nonrebreather face mask. The nurse informs you that his oxygen saturation was 68% on room air. He currently has heavily labored breathing and appears cyanotic. The nurse informs you that the patient was admitted 2 days ago for a severe COPD exacerbation. You decide to emergently intubate the patient. Which of the following will reduce the risk of developing pneumonia in this patient?
A. Place the patient in a semi-recumbent position
B. Avoid daily attempts to wean the patient from the ventilator

C. Measure daily gastric residual volumes

D. Administer daily omeprazole

E. Avoid any instrumentation of the airway, including endotracheal suctioning

Answers

1. **Answer: E. Small cell carcinoma.** The patient most likely has small cell carcinoma given the main risk factor of a strong smoking history, a mass located in the central/proximal airways and the muscle weakness suggestive of paraneoplastic Lambert–Eaton syndrome (also known as Eastern–Lambert syndrome, or Lambert–Eaton myasthenic syndrome). Other associated paraneoplastic syndromes with small cell include Cushing's and SIADH.

   Bronchial carcinoid is not clearly associated with smoking or Lambert–Eaton, although usually presents as a central/proximal lesion. Large cell carcinoma is not associated with Lambert–Eaton. Squamous cell carcinoma is not associated with Lambert–Eaton but is typically a central lesion; this lung malignancy is also the most likely lung cancer associated with paraneoplastic hypercalcemia.

2. **Answer: D. Obtain contrast-enhanced CT of the abdomen.** The patient is presenting with typical signs/symptoms of acute diverticulitis—fever, leukocytosis, LLQ location of pain. Further suggestion is made by the fact that the patient had a prior episode of rectal bleeding, likely from underlying diverticulosis. CT scan will help not only confirm the diagnosis but also to rule out other processes and assess for any complications of diverticulitis.

   Checking the serum lactate will help assess for ischemia but will not help you confirm the diagnosis of diverticulitis. Retroperitoneal ultrasound will assess for hydronephrosis and pyelonephritis but urinalysis/chemistry are normal and there is no suggestion of obstruction/infection regardless of his history of nephrolithiasis. Colonoscopy should be avoided in a patient with acute diverticulitis because of the risk of perforation. Proceeding to the operating room would be premature unless the patient had surgical indications such as

signs of peritonitis, fistula, stricture, large abscess, or perforation related to the diverticulitis.

3. **Answer: B. Heparin.** IV UFH (unfractionated heparin) and subcutaneous LMWH (low–molecular-weight heparin) are shown to decrease mortality in acute coronary syndrome. In addition, statins, ASA, and β-blockers (provided the patient is not in acute decompensated heart failure), and $P2Y_{12}$ inhibitors are also mainstays of therapy. ACE inhibitors are recommended prior to discharge.

   Alteplase is NOT indicated for UA/NSTEMI but ONLY for STEMI when PCI is *not* available. Hydralazine, furosemide, and digoxin offer no mortality benefit in this setting either.

4. **Answer: C. Aspirin.** Aspirin is shown to reduce recurrent stroke and to decrease mortality and should be administered within 48 hours.

   Insulin is not necessary as the level of glucose elevation is not contributing to the current presentation; in fact, aggressive glycemic control is associated with worse outcomes. Heparin has not been shown to improve outcomes and is not recommended as an acute treatment for ischemic stroke. Alteplase can be considered but only for significant deficits when the patient presents within 4.5 hours of clearly defined symptom onset and has no contraindications; this patient presented too late for this to be a treatment option. Labetalol would not be used despite the elevated BP as permissive hypertension is allowed in the setting of an acute ischemic stroke; BP up to 220/120 mm Hg is generally tolerated initially, unless the patient is a candidate for alteplase, in which case the blood pressure goal is systolic BP ≤185 and diastolic BP <110.

5. **Answer: E. Methylmalonic acid level.** The other answers will help narrow down your differential but will not definitely confirm the diagnosis. The patient has a total gastrectomy and thus loss of intrinsic factor leading to impaired absorption of B_{12}. The neurologic symptoms are a result of this deficiency and the fatigue/pallor are related to macrocytic anemia. Laboratory assessment of B_{12},

methylmalonic acid, or homocysteine would all be useful to confirm deficiency; however, homocysteine is also elevated in folate deficiency and thus not as specific. An elevated methylmalonic acid is specific to B_{12} deficiency.

Folate level could help confirm a deficiency in this vitamin which does cause a macrocytic anemia but this deficiency is not associated with neurologic deficits; in addition, folic acid is absorbed in the small intestine, not the stomach. CBC with mean corpuscular volume may help confirm macrocytic anemia but this is not always present with B_{12} deficiency; in addition, there are multiple causes of macrocytosis and anemia and this will not confirm his diagnosis. Intrinsic factor Ab is present in pernicious anemia; it is not a sensitive test but regardless, a positive test would not confirm the cause of his symptoms. MRI lumbar spine has nonspecific findings in B_{12} deficiency; it may help assess for central/foraminal stenosis but without back pain this is unlikely and would this test would not assess his pallor/anemia.

6. **Answer: D. 24-hour urine-free cortisol.** The patient likely has Cushing syndrome given the constellation of weight gain, striae (without prior history of pregnancy), new-onset diabetes, hypertension, and vertebral compression fracture indicative of osteoporosis. The diagnosis of Cushing syndrome requires that at least two of the three first-line tests are positive. These include a 24-hour urine-free cortisol level, a low-dose dexamethasone suppression test, or a late night salivary cortisol level.

Serum ACTH is not used for screening and is only helpful in determining the etiology once the diagnosis of Cushing syndrome has been made. It helps establish ACTH-dependent from ACTH-independent etiologies, narrowing the differential diagnosis and subsequent evaluation. MRI brain and CT abdomen may help identify pituitary adenoma and adrenal adenoma, respectively, but this test is premature at this point as the diagnosis of Cushing syndrome has not yet been confirmed. CRH stimulation test is only used once

hypercortisolism has been established and ACTH is elevated as it helps distinguish Cushing disease versus ectopic ACTH production.

7. **Answer: B. Intravenous fluids.** The patient is presenting with an inferior MI as evidenced by the location of the ST elevations on ECG. Because the patient also has bradycardia and hypotension, he also has evidence of an associated right ventricular MI, which is strongly associated with inferior wall MIs and importantly is treated differently than a left-sided MI. The diagnosis can be confirmed with a right-sided ECG, which would show ST elevations in V3R-V6R. It is important to remember that hemodynamic instability can result from increased vagal tone and sinus node dysfunction. Patients with right ventricular MI are often preload dependent and IV fluids are indicated to increase the systemic blood pressure. Treatment with antiplatelet agents (ASA and $P2Y_{12}$ inhibitors), fibrinolysis versus PCI, and anticoagulation (heparin or LMWH) are all indicated as well.

   Nitroglycerin will decrease preload and worsen the patient's hemodynamics. Furosemide is not indicated as the patient has no signs of fluid overload and diuresis will further decrease preload. The patient is already showing signs of hemodynamic instability and metoprolol will cause further bradycardia and hypotension. At this time, morphine may cause vasodilation and further hypotension. Morphine would be a reasonable choice once the patient is fluid resuscitated, as achieving pain control is very important in acute MI management.

8. **Answer: D. Sodium bicarbonate.** The patient has evidence of an anion gap metabolic acidosis (HCO_3 is decreased and AG is 15) as well as a respiratory alkalosis (CO_2 is decreased) consistent with salicylate toxicity. This involves using Winter's formula and the expected PCO_2 in this example is 31 ± 2; however, the actual PCO_2 is 25 confirming there is a respiratory alkalosis as well. Treatment options include alkalinization of urine with intravenous sodium carbonate, and hemodialysis for severe cases.

Fomepizole is indicated for methanol or ethylene glycol toxicity; however, neither of these would also cause respiratory alkalosis. Albuterol will treat a COPD exacerbation, although CO_2 retention and primary respiratory acidosis would be the dominant finding in that scenario. Insulin would be the treatment for diabetic ketoacidosis (DKA). However, DKA would present with a primary anion gap metabolic acidosis, hyperglycemia, and hyperosmolarity, and this clinical picture is more consistent with salicylate toxicity.

9. **Answer: E. Colonoscopy.** The patient has not had colorectal cancer screening and this would certainly be indicated at this time given his age (>45). Initial choices for screening include FIT, flexible sigmoidoscopy, or colonoscopy. In this example, the patient had a positive screening test and requires a colonoscopy as it will allow full visualization of the entire colon for diagnostic and therapeutic (biopsy if needed) purposes.

   Flexible sigmoidoscopy will miss more than half of the colon and therefore is not the best answer. Digital rectal examination will not be sensitive enough to check anything but the rectum. Video capsule endoscopy is not the best next step; it will allow visualization of the entire GI tract but will not allow for biopsy if needed. CT colonography will not be sensitive enough to detect small lesions and again will not allow for intervention if necessary.

10. **Answer: A. IV omeprazole.** The patient likely has an upper GI bleed as evidenced by epigastric abdominal pain, melena, and labs showing an elevated BUN:Cr ratio of >30 in the setting of NSAID use. Acid suppression and upper endoscopy (EGD) are the indicated interventions.

    IV octreotide is not indicated as the patient has no signs of cirrhosis (e.g., thrombocytopenia, coagulopathy) to suggest esophageal varices as the cause of bleeding. Platelet transfusion will not reverse the effect aspirin has had on platelets and the patient does not have thrombocytopenia that would necessitate platelet transfusion during bleeding. RBC transfusion is not necessary as the patient is hemodynamically stable and the Hgb is not below the recommended

transfusion threshold (usually Hgb < 7 g/dL, or higher in those with active cardiac disease, symptomatic anemia, or ongoing bleeding). IV fluids are not necessary at this point as the patient does not appear hypovolemic or hemodynamically unstable.

11. **Answer: E. 24-hour urine protein.** The patient has ascites in the setting of a low SAAG (<1.1 g/dL) indicating the etiology is not portal hypertension, and low ascitic protein (<2.5 g/dL) indicating low protein overall. The expected diagnoses would be severe malnutrition or protein-losing disorder such as nephrotic syndrome; thus, 24-hour urine protein is the most appropriate test. Moreover, she has hypercholesterolemia and physical examination evidence of a deep vein thrombosis, both of which can result from nephrotic syndrome.

    Echocardiogram would be helpful if the patient had elevated SAAG and elevated ascitic protein, which is consistent with cardiac ascites. Pelvic ultrasound to assess for potential ovarian malignancy would be indicated if patient had low SAAG and elevated ascitic protein. Liver biopsy might be indicated to assess for causes of cirrhosis if patient had elevated SAAG and low ascitic protein. Adenosine deaminase of the ascites fluid is one of several tests that can be used in the diagnosis of peritoneal tuberculosis, which would be more likely if patient had low SAAG and elevated ascitic protein.

12. **Answer: B. IVIG.** The patient is presenting with an ascending paralysis, absent reflexes, and albuminocytologic dissociation (elevated CSF protein, but normal cell count) consistent with a diagnosis of Guillain–Barré syndrome in the setting of a preceding diarrheal illness. IVIG and plasma exchange are the recommended treatments.

    Prednisone is not recommended as steroids have not shown benefit. Ciprofloxacin is not indicated as there are no signs of ongoing infection; there are many precipitating illnesses that can trigger this disorder. Pyridostigmine would be indicated in myasthenia gravis. Botulism antitoxin would be beneficial if the patient has symptoms suggestive of botulism, a descending paralysis.

13. **Answer: E. Ristocetin cofactor activity.** The patient is presenting with mucocutaneous bleeding suggestive of von Willebrand disease. vWD is an autosomal dominant disorder and can be associated with factor VIII deficiency, sometimes manifested by an increased PTT level. Ristocetin testing is the only test mentioned that assesses platelet aggregation.

Fibrinogen levels can be low in DIC but these patients are usually acutely ill and PT/PTT would also be elevated. Direct antiglobulin test (DAT) will assess for causes of hemolytic anemia but not for bleeding; in addition, bilirubin is normal suggesting against hemolysis. Factor IX level is helpful in diagnosis of hemophilia B, but this diseases is X linked recessive and unlikely to be seen in successive generations of females; in addition, hemarthrosis or hematomas would be more prominent. A mixing study is not indicated as the PT/PTT times are normal, so the patient is unlikely to have a factor deficiency or inhibitor.

14. **Answer: E. Lumbar puncture.** The patient has acute headache in "thunderclap" fashion and subarachnoid hemorrhage is a must-not-miss diagnosis. CT brain showed no signs of hemorrhage, but LP is the next best step to evaluate for RBCs, xanthochromia, or an elevated opening pressure (all signs of SAH).

Sumatriptan can be used for migraines but his symptoms are not suggestive of migraines, and it is necessary to rule out SAH with this patient's concerning history. MRI brain may have comparable sensitivity to CT scan, but a negative scan should still be followed by a lumbar puncture for definitive evaluation. Cerebral angiogram will be useful once SAH is confirmed, but is invasive and will not be the next step. CT brain with contrast is unlikely to visualize a small aneurysm and is not the next step.

15. **Answer: A. Smoking cessation.** She has evidence of obstructive pulmonary disease as indicated by her FEV_1/FVC ratio <0.70. Smoking cessation will decrease the rate of decline in lung function and is one intervention for COPD that has also been shown to decrease mortality.

Tiotropium and salmeterol are likely to improve her symptoms but will have no effect on mortality. Oxygen therapy has been shown to decrease mortality but is only indicated if O_2 saturation is 88% or below at rest, or if 89% or below combined with evidence of cor pulmonale, right heart failure, or erythrocytosis. Azithromycin is indicated in the treatment of COPD exacerbation, and is considered for severe COPD when other therapies have not been effective. The best long-term intervention for this patient is smoking cessation.

16. Answer: B. Wisdom tooth extraction. Endocarditis prophylaxis requires a high-risk situation PLUS a qualifying procedure that is high risk for bacteremia and resultant endocarditis. Antibiotic prophylaxis is currently recommended for the following cardiac conditions: certain congenital heart diseases, history of infective endocarditis, valve disease in a heart transplant patient, and presence of a prosthetic valve. Thus, this patient should receive prophylaxis since he has a prosthetic valve and is undergoing a dental procedure.

Colonoscopy, EGD, as well as GI procedures in general do not require prophylaxis. Bronchoscopy only requires prophylaxis if mucosa will be broken, such as with biopsy. Dilatation ureteral strictures as well as GU procedures in general do not require antibiotics to prevent endocarditis (although antibiotics may be indicated for asymptomatic bacteriuria prior to GU procedure).

17. Answer: A. SPEP (serum protein electrophoresis). The patient is presenting with a pathologic fracture, indicating weakening of the underlying bone prior to a low impact injury. The laboratory findings (hypercalcemia, normocytic anemia, renal failure, and low anion gap) are suggestive of multiple myeloma; thus, SPEP would be the best next step in diagnosis.

Bone scans detect osteoblastic activity and can be falsely negative in myeloma. PTHrP can assess for hypercalcemia of malignancy, but this clinical scenario is more concerning for multiple myeloma than malignancy. In addition, an elevated PTHrP would explain only the hypercalcemia. PTH elevation in hyperparathyroidism would explain the hypercalcemia, but not the other lab findings. A DEXA scan is

useful to evaluate for underlying osteoporosis, but the x-ray shows normal bone density, and it is more likely that his pathologic fracture is related to a lytic lesion from multiple myeloma.

18. **Answer: E. TSH.** The patient has symptoms suggestive of hypothyroidism (bradycardia, fatigue, weight gain, hair loss) and TSH is the best initial screening test.

US thyroid is not necessary when the physical examination is normal. TPO would help confirm Hashimoto's as a potential cause of hypothyroidism but would not help confirm hypothyroidism itself, as patients may have elevated antibodies but normal thyroid function. Thyroid uptake scan would be more helpful in evaluating hyperthyroidism, such as thyroiditis or Graves disease. FNA is only indicated if a patient has a nodule with size or features worrisome for malignancy and in need of tissue diagnosis.

19. **Answer: A. Follow-up CT chest.** The patient has an indeterminate pulmonary nodule discovered incidentally that requires further follow-up. The patient is low risk (<5%) as evidenced by her lack of smoking history and young age. Interval CT scan is the most appropriate follow-up (Fleischner guidelines and ACCP guidelines). Of note, if the nodule clearly has benign properties such as popcorn calcifications suggesting hamartoma, no further follow-up is required.

Bronchoscopy and needle biopsy are indicated if the patient had an intermediate/high malignancy risk, if the nodule is enlarging, or the patient desires a definitive tissue diagnosis. CXR is not sensitive enough to follow changes in size. PET-CT scan may also be indicated if there is intermediate/high risk of malignancy.

20. **Answer: D. Atropine.** The patient has symptomatic bradycardia with hypoperfusion leading to her symptoms; atropine is the first step in resuscitation for symptomatic bradycardia. If atropine is ineffective, then epinephrine, dopamine, or transcutaneous or transvenous pacing would all be alternative treatments.

Echocardiogram will not help treat the patient in the acute setting as this situation demands urgent intervention; obtaining this test will

only delay treatment. Nitroglycerin can be used to alleviate chest pain, but will cause decreased preload and thus worsen this patient's hypotension. ICD is a consideration for this patient for long-term primary prevention of ventricular arrhythmias with her reduced EF despite maximal goal-directed medical therapy; however, it is not an acute treatment for the patient's life-threatening condition.

21. **Answer: E. Trial of omeprazole.** His symptoms are suggestive of gastroesophageal reflux with a component of laryngeal reflux. He is currently only using an H_2 blocker as needed. PPIs are more effective than H_2 blockers; if his symptoms persist despite a PPI for 8 weeks, then workup should be done for other causes of his symptoms.

Helicobacter pylori antigen would be useful if evaluating for abdominal pain if gastritis/ulcers were the suspected diagnoses. EGD would be indicated if patient was following lifestyle changes and taking scheduled PPI but having no relief in symptoms, or if he had alarm symptoms (melena, anemia, weight loss, or dysphagia). pH monitoring can also be used for refractory symptoms after appropriate empiric therapy. Gastrin level would only be indicated if evaluating for suspected gastrinoma or with multiple gastroduodenal ulcers.

22. **Answer: A. EGD with small bowel biopsy.** The patient has chronic symptoms suggestive of celiac sprue (iron deficiency, mildly elevated transaminases, anemia, and dermatitis herpetiformis). There is also an association with psychiatric issues with celiac sprue. TTG serology would be reasonable and duodenal biopsy is necessary for confirmation.

Colonoscopy would not be able to evaluate for a diagnosis of celiac sprue. Loperamide may help diarrhea but will not address the underlying cause of her symptoms and is therefore not the best answer. Sertraline would be helpful in pharmacologic treatment of depression; there is a link of IBS with mood disorders but IBS is a diagnosis of exclusion and only considered when labs/examination is normal. Skin biopsy may confirm dermatitis herpetiformis but small

bowel biopsy is still be needed for the diagnosis of celiac sprue, as one may have this skin condition without having celiac disease.

23. **Answer: B. Spironolactone.** The patient has NYHA class IV heart failure with reduced ejection fraction (HFrEF) and MRAs such as spironolactone are shown to decrease mortality in these patients. β-Blockers, ACEi/ARB, ARNI (angiotensin receptor/neprilysin inhibitor), SGLT2 inhibitors, and ICDs are also shown to decrease mortality in patients with heart failure with reduced ejection fraction.

Isosorbide dinitrate and hydralazine are alternatives to ACEi/ARBs for afterload reduction if the patient cannot tolerate one of those agents, but do not have mortality benefit. Digoxin and furosemide may be helpful for symptoms but do not decrease mortality in heart failure.

24. **Answer: D. Inhaled albuterol PRN.** The patient has classic symptoms of exercise-induced bronchoconstriction and would benefit from pre-exercise inhaler usage to prevent symptoms. It is important to remember that PFTs may be normal between episodes when the patient is asymptomatic; a challenge may be needed to objectively evaluate the bronchoconstriction.

CXR is not necessary as the lung examination is clear and she has no symptoms at baseline. Inhaled fluticasone is not the best answer as the patient only has intermittent symptoms related to activity, not constant symptoms to suggest chronic asthma. Reassurance is not appropriate as the patient clearly has symptoms that limit her lifestyle and are causing airway constriction. Inhaled salmeterol is not appropriate as the patient has no baseline symptoms between episodes; in addition, treatment of asthma with LABA monotherapy, without cotreatment with inhaled corticosteroids, has been found to be associated with increased serious adverse events.

25. **Answer: D. No treatment.** It is not recommended to screen for asymptomatic bacteriuria as treatment does not offer benefit but does include potential harm from inappropriate use of antibiotics. The only populations in which to screen and treat asymptomatic bacteriuria are

pregnancy and patients undergoing urologic procedures in which mucosal bleeding is expected (some experts recommend treatment in patients with history of renal transplantation, but this is controversial).

Nitrofurantoin would be the drug of choice for a patient with uncomplicated cystitis. Cephalexin and TMP-SMX would be considerations for cystitis or for pyelonephritis. Repeat urinalysis and culture is not indicated as screening and treating asymptomatic bacteriuria in this patient would not offer clinical benefit.

26. **Answer: B. IV hydrocortisone.** The patient is presenting with acute adrenal crisis, which is an endocrine emergency. The patient must be adequately resuscitated with IV fluids in addition to replacement of corticosteroids. The most likely cause for the patient's adrenal insufficiency is her long-term use of corticosteroids and inadequate response in the setting of acute illness.

A cortisol level can be checked but medical treatment is the most important intervention, and it is not necessary to confirm a low cortisol in a patient with this constellation of signs and symptoms of adrenal crisis. CT adrenal glands and MRI pituitary are unlikely to yield further information regarding the diagnosis in the patient; in addition, they would be inappropriate as they would delay the treatment of the patient and lead to higher morbidity/mortality. Cosyntropin stimulation test can be used to confirm the diagnosis of adrenal insufficiency but should NOT delay treatment; dexamethasone could be used if the diagnosis is in question as it will not interfere with interpretation of this test.

27. **Answer: A. CT angiography.** The patient has pain out of proportion to examination in the setting of atherosclerotic risk factors for thrombosis as well as atrial fibrillation with intermittent adherence to anticoagulation, which are risk factors for embolism. The most likely diagnosis is acute mesenteric ischemia and CT angiography is the best diagnostic study to confirm diagnosis.

Gastric emptying study would be helpful to evaluate for gastroparesis, which the patient is at risk for with poorly controlled diabetes; however, this patient is presenting with acute abdominal

pain, which is not consistent with the presentation of gastroparesis. EGD and colonoscopy would help evaluate for many causes of abdominal pain but would delay the diagnosis of acute mesenteric ischemia, which is needed urgently to prevent bowel infarction. Andexanet alfa can rapidly reverse apixaban in the setting of major bleeding, but given the scenario suggestive of acute mesenteric ischemia and stable hemodynamics, rapid reversal is not indicated at this time. Rapid reversal of anticoagulation may be needed if the patient develops bowel infarction/necrosis and needs emergent surgery.

28. **Answer: E. Ibuprofen.** NSAIDs are the mainstay of treatment for acute pericarditis. Colchicine can be added to this regimen for added benefit.

Coronary angiogram is not indicated as there are no focal ST elevations or wall motion abnormalities suggestive of an acute MI. Drainage of pericardial effusion is only indicated in large or rapidly accumulating effusions causing hemodynamic compromise or for diagnostic purposes. Prednisone is not indicated unless NSAIDs are not effective or the patient has contraindications to receiving them. Azathioprine would only be used if the patient had recurrent pericarditis and was unable to wean off of steroids.

29. **Answer: C. Chest tube insertion.** It is important to recognize that the patient is presenting with a symptomatic spontaneous pneumothorax, in this setting related to his underlying COPD and likely bleb rupture. CXR can confirm the diagnosis, but this can also be made clinically. Supplemental oxygen would be appropriate followed by needle aspiration or chest tube insertion to remove air from the pleural space.

Albuterol–ipratropium nebulizer and prednisone would help treat COPD exacerbation but this is not the diagnosis presented. Azithromycin is not the best answer as there is no suggestion of infection in this patient. Pleurodesis is only indicated if there are recurrent pneumothoraces.

30. Answer: D. Warfarin. The patient has atrial fibrillation and a CHADS2-VASc score of 4 without a history of major bleeding, thus warranting systemic anticoagulation. In addition, the patient has a mechanical aortic valve. For most patients with atrial fibrillation, a direct oral anticoagulant (DOAC) is an appropriate choice for systemic anticoagulation. However, patients with mechanical valves should be on warfarin.

Aspirin and clopidogrel are antiplatelet agents that are not adequate as for this patient with an elevated CHADS2-VASc score. Apixaban and dabigatran are DOACs that would be appropriate if the patient did not have a mechanical valve.

31. Answer: B. Aortic valve replacement. The patient has symptomatic aortic stenosis which is an indication for valve replacement. Options include a surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR).

Nitroglycerin would be indicated if his symptoms were related solely to atherosclerotic disease; however, vasodilation may worsen his systemic blood pressure. Aspirin will prevent further atherosclerotic disease but will not fix his valvular disease. Carotid Doppler will assess for carotid stenosis; however, the murmur heard in the neck is referred from the aortic valve. Coronary artery bypass grafting is sometimes done at the same time as a surgical valve replacement if significant atherosclerotic disease is present; however, he has very mild disease on prior angiogram and this is not indicated.

32. Answer: B. Physical therapy. The diagnosis here is patellofemoral pain syndrome and PT is the most appropriate intervention.

Corticosteroid injection would be unlikely to be helpful as the cause of pain is not intra-articular; she does have an underlying autoimmune disease but there is no effusion and inflammatory markers do not show significant inflammation to heighten suspicion of SLE as the cause. Knee arthroscopy and MRI knee are also unwarranted at this time given the normal examination and lack of trauma to suggest meniscal or ligamentous injury. Ibuprofen is contraindicated given CKD.

33. Answer: E. Lisinopril. The patient has a new diagnosis of type 2 diabetes with elevated blood pressure and requires not only control of his glucose but also treatment for complications related to his disease. An ACE inhibitor or ARB are indicated for hypertension, CKD, or moderately increased albuminuria, and thus lisinopril is the best answer.

Hydrochlorothiazide, amlodipine, and hydralazine are not the best choices for antihypertensives as they do not have renal protective features that ACE inhibitors do. Insulin is not necessary given the patient's relatively controlled A1c and is premature at this point without trialing lifestyle modifications first.

34. Answer: E. Bronchoscopy and biopsy of hilar lymph node. The patient's clinical picture is consistent with possible sarcoidosis. Tissue biopsy showing noncaseating granulomas along with ruling out other diseases is essential for the diagnosis.

Serum calcium will be elevated in a subset of sarcoid patients but this is not sensitive enough to make the diagnosis. CT chest will yield more information in regard to lung imaging but will not confirm a diagnosis. A serum ACE level is not sensitive enough to confirm a diagnosis (it may be normal in sarcoidosis). Biopsy of a leg lesion which is easily accessible will reveal inflammation as the patient has findings consistent with erythema nodosum; however, this will not show noncaseating granulomas so this will not confirm a diagnosis of sarcoid.

35. Answer: B. Initiate fluid restriction. The patient is euvolemic and has low serum osmolality, and high urine osmolality which are all suggestive of SIADH due to underlying lung cancer as the cause. He has very mild symptoms and can be managed with fluid restriction. Oral salt tabs or oral urea packets (both of which provide a high solute load, which promote free water excretion) may be useful for management as well.

Administering IV normal (0.9%) saline is not the appropriate answer as sodium will be excreted but water will be retained; thus, worsening hyponatremia. Initiating hemodialysis is not appropriate as

the patient has minimal symptoms, has not failed other therapies, and is overly invasive. Administering hypertonic (3%) saline is not necessary as the patient has minimal symptoms; if the patient had severe symptoms such as confusion, lethargy, nausea, or vomiting this would be appropriate. Administering hydrochlorothiazide is not correct as this medication itself can worsen hyponatremia.

36. **Answer: D. Antistreptolysin titer.** The patient is presenting with hematuria in the setting of a recent infection and the most likely diagnosis is poststreptococcal glomerulonephritis. Antistreptolysin titer can help confirm recent strep infection.

ANCA is unlikely to be helpful as the patient does not have other symptoms suggestive of a systemic vasculitis. Anti-GBM is also unlikely to assist in the diagnosis as the patient has no other symptoms to suggest this and the time course fits best with PSGN. HIV is associated with renal disease, most specifically collapsing variant of FSGS but this is nephrotic in presentation. IgA levels are unnecessary as serum IgA levels are not useful in the diagnosis of IgA nephropathy; in addition, the glomerulonephritis associated with IgA deposits happens much quicker after the infection, usually within several days.

37. **Answer: E. SLE.** This patient has multiple symptoms and examination findings consistent with a likely diagnosis of SLE—oral ulcers, malar rash, arthritis, edema suggestive of renal impairment, as well as hematologic abnormalities.

Osteoarthritis is unlikely given the patient's young age and would not explain the patient's multiple other symptoms. Reactive arthritis usually follows a GI/GU infection and includes arthritis, urethritis, and uveitis. Behçet disease can include many symptoms, most notably oral/genital ulcerations but would be unlikely to include the classic malar rash and is very rare in the United States. Gout is possible given her use of HCTZ and potential for hyperuricemia but this would not explain the other findings.

38. Answer: B. Carbidopa–levodopa. The patient is presenting with symptoms consistent with Parkinson disease and medical treatment is recommended with dopamine agonist.

Fluoxetine is not appropriate as the patient does not have a clinical diagnosis of depression; his psychomotor slowing alone should not be misinterpreted as depressive symptoms unless there are other symptoms such as sadness, appetite changes, sleep disturbance, or disinterest in activities. Propranolol can be beneficial in patients with essential tremor. Memantine is indicated only if patient has moderate-to-severe dementia. Deep brain stimulation is invasive and would not be considered unless severe symptoms develop or medical therapy is no longer effective.

39. Answer: C. Infliximab. The patient has moderate-to-severe Crohn disease (anemia, abdominal tenderness, and weight loss) and demands appropriate therapy to prevent complications. Infliximab is an anti-TNF antibody that is indicated for moderate-to-severe Crohn disease.

Loperamide should not be used in active inflammatory bowel disease. Azathioprine is less likely to offer control of the patient's symptoms than infliximab (although it may be used in combination with infliximab); in addition, this medication takes up to 6 weeks to reach a therapeutic effect and needs to be given alongside steroids. Surgical resection is not indicated as the patient has no evidence of abscess, perforation, or fistula. Ciprofloxacin and metronidazole are not indicated for treatment of active Crohn disease without signs of infection.

40. Answer: A. Thumb spica splint. The patient has risk factors for several causes of pain related to overuse in the upper extremity but examination reveals a positive Finkelstein test which confirms a diagnosis of de Quervain tenosynovitis. This is related to a combination of repetitive motions in this patient's occupation as mechanic and in caring for his grandchild. Immobilization of the thumb is the most appropriate intervention.

Wrist splint would be helpful if the patient had carpal tunnel syndrome. Counterforce forearm brace would be helpful if patient had

lateral/medial epicondylitis. Carpal tunnel corticosteroid injection is not helpful as this is not the source of his pain. Ibuprofen is contraindicated given his known chronic kidney disease.

41. **Answer: B. Reduction of fracture.** The patient has the classic triad diagnostic for fat embolism: hypoxia, petechial rash, and neurologic abnormalities. Treatment is supportive and as the source of emboli is her multiple long bone fractures; these should be repaired when the patient is stabilized.

Albuterol is not indicated as the patient has no evidence of obstructive lung disease (e.g., wheezing) as a cause for her acute decline. Furosemide is not indicated as the patient has no evidence of volume overload. Levofloxacin is not indicated as there is no evidence of infection. IV heparin will be ineffective in improving the patient's symptoms as it cannot dissolve fat, only thrombi.

42. **Answer: A. Valsalva maneuver.** The patient has SVT likely related to AVNRT and he is hemodynamically stable with no concerning symptoms. Initial attempt at termination should use vagal maneuvers such as Valsalva maneuver.

Adenosine is very short acting and can be used if vagal maneuvers fail to terminate the arrhythmia. Metoprolol would also be considered if the above measures failed. Digoxin would also inhibit the AV node but has more potential side effects than the other medications and is rarely used for this purpose. Cardioversion is reserved for signs of hemodynamic instability including hypotension, heart failure, or angina.

43. **Answer: D. Methotrexate.** The patient is presenting with signs/symptoms fulfilling criteria for a diagnosis of rheumatoid arthritis. The most important intervention is DMARD therapy (disease-modifying antirheumatoid drugs), especially as the patient already has evidence of joint damage.

Prednisone, corticosteroid injections, and indomethacin will all help control symptoms but not control joint damage. Physical therapy

will help improve function for the patient but without DMARD therapy her joint damage will continue to worsen.

44. **Answer: C. ERCP.** The patient has cholangitis secondary to obstructing common bile duct stone and is presenting with severe sepsis. The patient needs hemodynamic support, antibiotics, and control of the source of infection. ERCP is the next step in order to relieve the obstruction and allow drainage of the biliary system.

Cholecystectomy is recommended eventually to prevent recurrence but not in the acute setting due to higher morbidity and mortality. Liver biopsy will not aid in diagnosis or treatment; the cause of elevated tranaminases is evident. MRCP may be helpful to clarify if the stone is still obstructing the common bile duct in equivocal cases, but in this case, her worsening transaminases and hyperbilirubinemia indicate ongoing obstruction. Percutaneous transhepatic cholangiography is second line to ERCP as it carries higher morbidity in regard to bleeding or peritonitis.

45. **Answer: E. No further intervention.** There is no further workup or treatment that is required at this point. The patient is in a low-risk category with no identifiable risk factors and a PPD is considered positive if 15 mm or greater in the absence of risk factors.

AFB sputum culture is not necessary to rule out active pulmonary TB because the patient is asymptomatic and has a negative PPD test. Rifampin, isoniazid, pyrazinamide, ethambutol would be indicated only if the patient had active pulmonary TB. Rifampin alone would be indicated for treatment of latent infection if the patient had a positive TB test without any pulmonary symptoms and a negative CXR. Chest x-ray would be indicated to evaluate for evidence of pulmonary TB if the PPD was positive.

46. **Answer: B. PTH.** The patient has calcium pyrophosphate dehydrate deposition disease (CPPD, pseudogout). This is confirmed by the inflammatory arthrocentesis with CPPD crystals and imaging findings showing deposition. Associated disorders include hemochromatosis, hyperparathyroidism, and hypothyroidism, so labs including calcium,

phosphorus, magnesium, PTH, TSH, and an iron panel are all reasonable to screen for as treatment of underlying disorder can improve symptoms. This is especially important in patients who are diagnosed with CPPD at a young age.

Uric acid would be helpful in determining initial treatment for gout, but this is not the underlying diagnosis. ANA and ESR are nonspecific and would not be helpful in guiding therapy. HLA-B27 is not indicated as the diagnosis of CPPD is confirmed and this will not screen for any associated disease.

47. **Answer: A. Zoledronic acid.** The patient has osteoporosis and a history of a fracture; thus, every attempt would be made to start the patient on a medication to reduce her risk of fractures. Zoledronic acid is a bisphosphonate which will reduce both vertebral/nonvertebral fractures; in addition, it is given intravenously and is most appropriate in this patient with achalasia.

Alendronate is a PO bisphosphonate and should be avoided in achalasia due to the risk of pill esophagitis. Raloxifene is a selective estrogen receptor modulator (SERM) and has evidence only for reduction of vertebral fractures and would thus not be an ideal choice; in addition, it should be avoided in this patient as it increases risk of venous thromboembolism (VTE). Calcitonin can be used for treatment of osteoporosis but is less effective than bisphosphonates so should not be first-line therapy. Estrogen is no longer used for management of osteoporosis in light of its many adverse effects, including increased rate of VTE.

48. **Answer: D. Propranolol.** The patient is presenting with thyroid storm, an endocrine emergency, and requires treatment without delay. She now also has atrial fibrillation with rapid ventricular response, likely triggered by increased adrenergic tone from thyroid storm. This was likely triggered by her recent surgery. β-Blockers like propranolol will control the tachycardia induced by increased adrenergic tone.

RAIU at this point will delay treatment which is not appropriate given the morbidity/mortality associated with thyroid storm. Iodine is a treatment option used in thyroid storm; however, it should be given

AFTER methimazole or PTU to avoid its use as a substrate for more thyroid hormone synthesis. US thyroid is also unnecessary and will delay treatment. Thyroidectomy should only be performed once the hyperthyroidism is treated given the mortality rate associated with surgery in thyroid storm.

49. **Answer: A. CT urography.** The patient has hematuria and whether gross or microscopic hematuria, this demands further workup. A negative urine culture and absence of pyuria make infection unlikely. The urinalysis is also not consistent with a glomerular cause. All patients with hematuria without evidence of infection or glomerular disease should undergo cystoscopy and CT urography to evaluate for malignancy or other causes of bleeding.

Ultrasound of kidneys and bladder will evaluate the kidneys and bladder but can miss small tumors and will be less sensitive in evaluating the ureters. Renal biopsy is not indicated in this scenario as a glomerular source of bleeding is unlikely; RBC casts or dysmorphic RBCs on microscopy would be suggestive of a glomerular cause. PSA and prostate biopsy are unlikely to yield a cause of the patient's bleeding and would not evaluate the remainder of the GU tract.

50. **Answer: D. Albuterol.** The patient has a diagnosis of acute bronchitis and this is most likely viral in nature. Symptoms are related to hyperreactive airways and should self-resolve in a few weeks; treatment is symptomatic. Because of the wheezing associated with his symptoms, albuterol would be the appropriate choice. Inhaled β-agonists such as albuterol are often limited for use in acute bronchitis to patients with wheezing or underlying pulmonary disease.

Prednisone is not indicated as the patient has no underlying reactive lung disease, is not in distress, and his peak flow is normal. Oseltamivir is not indicated because the patient does not have symptoms suggestive of influenza; in addition, he is well outside the appropriate window of treatment given his risk factors. Antibiotics are NOT indicated as the etiology of most acute bronchitis is viral; antibiotics would be indicated if pneumonia was confirmed. Sputum culture is not necessary as a viral cause is much more likely.

51. **Answer: B. Weight loss.** Most groups recommend the following lifestyle modifications for patients with hypertension: *Reducing dietary sodium* to less than 2.4 g per day; *increasing exercise* to at least 30 minutes per day (4 days per week); *limiting alcohol consumption* to 2 drinks or less per day for men and 1 drink or less per day for women; following the *Dietary Approaches to Stop Hypertension (DASH) diet* (high in fruits, vegetables, potassium, calcium, and magnesium; low in fat and salt); and achieving a *weight loss* goal of 10 lb (4.5 kg) or more. Of these, weight loss has shown to have the highest reduction in systolic blood pressure (reduction from 5 to 20 mm Hg) in overweight patients. **(A, C, D)** These three lifestyle modifications are also recommended and do have a substantial effect on reduction of systolic pressure, just not as much as weight loss does. **(E)** Smoking cessation should always be encouraged as part of any comprehensive lifestyle modification plan.

52. **Answer: A. Lisinopril.** This patient has type 2 diabetes and hypertension, so he should be on an ACE inhibitor or ARB. ACEi/ARB are shown to be renal protective in diabetes, so these should be first-line antihypertensives in all patients with concomitant diabetes. Thiazide diuretics such as hydrochlorothiazide or calcium-channel blockers such as amlodipine are first-line treatment in patients without diabetes **(B, C)**. β-Blockers such as atenolol or propranolol are not first-line therapy for hypertension **(D, E).**

53. **Answer: A. Pyelonephritis.** Pyelonephritis produces flank pain, but is also suggested by fever, leukocytosis, and a urinalysis showing infection (e.g., positive nitrites, positive leukocyte esterase). The presence of WBC casts is also seen in pyelonephritis, as is the physical examination finding of costovertebral angle tenderness (CVA) tenderness. **(B)** Nephrolithiasis (kidney stones) produces a colicky pain but uncomplicated nephrolithiasis typically does not produce fever, leukocytosis, or urinalysis findings suggestive of infection (however it does often cause hematuria). **(C)** Appendicitis is a very important diagnosis to consider in young patients with abdominal pain, however does not explain the positive urinalysis

findings. **(D)** Ectopic pregnancy can often mimic the pain produced in nephrolithiasis, however this diagnosis is unlikely given the negative pregnancy test. **(E)** Acute interstitial nephritis (AIN) can indeed cause fever and produce WBC casts in the urine, but her constellation of urinalysis findings is more supportive of an ascending urinary tract infection such as pyelonephritis. The most common cause of AIN is an allergic reaction to medications.

54. **Answer: C. Nonsteroidal anti-inflammatory drugs (NSAIDs).** Back pain that improves with exercise, but worsens with rest in an otherwise healthy young patient lends credence to the diagnosis of ankylosing spondylitis (AS). AS is a seronegative spondyloarthropathy (rheumatoid factor is negative) that is a systemic rheumatic disease. Ninety percent of people express the HLA-B27 genotype. It is also three times more common in males than females. In addition to back pain, patients can also experience anterior uveitis causing eye redness and pain, and cardiovascular and lung involvement. The first-line treatment for all seronegative spondyloarthropathies is NSAIDs, but biologics and disease-modifying antirheumatic drugs (DMARDs) are effective in treating the progression of the disease. **(A, B)** Local heat and ice therapy may be effective in back pain caused by musculoskeletal strain. This is a consideration in this patient, but the severity of his back pain that improves with exercise and worsens with rest, and lack of a known trigger make this less likely than AS. **(D, E)** Epidural steroid injections and surgical laminectomy are typically reserved for refractory back pain that does not respond to more conservative measures initially.

55. **Answer: E. Nebulized albuterol for bronchodilation.** This patient is likely suffering from an asthma exacerbation caused in part by his recent exposure to a viral illness. There were wheezes on examination with no urticaria or angioedema, making an anaphylactic reaction unlikely. **(C)** Management of an acute asthma exacerbation involves oxygen administration as well as intermittent or continuous nebulized albuterol, which is the first-line treatment. If albuterol is not effective,

then ipratropium and magnesium are additional options to promote bronchodilation. Oral corticosteroids should also be given to reduce airway inflammation during and after the exacerbation. Response to therapy can be monitored by following the SaO_2 as well as either the FEV_1 or the peak expiratory flow (PEF). Arterial blood gases may also be useful; be concerned about the finding of a normal $PaCO_2$, which is often indicative of respiratory fatigue leading to the need for intubation (hypoxemia should cause hyperventilation and hypocapnia). **(A)** Although the patient has signs of increased work of breathing, it would be premature to intubate the patient before trialing first-line therapies for an asthma exacerbation. **(B)** This patient is unlikely to have pneumonia as he is afebrile and has no suggestive findings of pneumonia on lung examination. **(C)** Subcutaneous epinephrine is useful in anaphylaxis, but has no benefit over inhaled β_2-agonists in asthma for bronchodilation. (**D**) Ipratropium is an anticholinergic and is the first-line treatment for COPD exacerbation (although albuterol is often used too); it may be used as an adjunctive therapy in asthma exacerbation, but albuterol is the first-line therapy.

56. **Answer:** C. ***Staphylococcus aureus*.** This patient's clinical presentation and subsequent deterioration are consistent with a diagnosis of toxic shock syndrome (TSS), which is caused by preformed *S. aureus* exotoxin, TSST-1. TSS was historically most often associated with prolonged tampon use, but is also associated with surgical wound infections, sinusitis, and many other common sites of infection. The toxin acts as a superantigen, which activates T cells leading to massive cytokine release. TSS typically presents with fever, vomiting, diarrhea, and the development of a diffuse macular erythematous rash. Complications of TSS include acute respiratory distress syndrome (ARDS), hypotension, disseminated intravascular coagulation (DIC), and hemorrhage. **(A)** *Escherichia coli* is not associated with TSS. **(B)** *Neisseria meningitidis* can certainly present with fever and diffuse rash, however it is not associated with such a high fever or tampon use. **(D)** *Streptococcus pneumoniae* is a type of group B Strep species, and accordingly, does not cause TSS. Only

Group A Strep species such as *Streptococcus pyogenes* can cause TSS. **(E)** Rocky Mountain spotted fever presents with fever and a rash that is first apparent in the extremities and moves centrally.

57. **Answer: B. Recurrent pericarditis.** The chest pain and ECG are typical of acute pericarditis, which commonly presents with fever, pleuritic chest pain, new-onset pericardial effusion, and diffuse concave ST elevations on ECG. Most cases have an infectious etiology, including Coxsackie viruses, HIV, influenza, *Staphylococcus aureus, Streptococcus pneumoniae,* tuberculosis, and various fungi. Other important causes include cancer, autoimmune diseases, post-MI or cardiac surgery, radiation therapy, and uremia. Acute pericarditis should be treated with NSAIDs and colchicine to improve symptoms and prevent complications. Patients who are not treated are much more likely to develop recurrent pericarditis, which is defined as a recurrence of symptoms after the inciting event (e.g., virus) has passed. **(A)** Pericardial effusions commonly accompany acute pericarditis, but cardiac tamponade is a rare complication. **(C)** Constrictive pericarditis is a possible outcome of any cause of acute pericarditis, but is not the most common complication. **(D)** Free wall rupture is a complication of acute myocardial infarction. (**E**) Pericarditis affects the pericardium, although the myocardium is sometimes affected as well in perimyocarditis or myopericarditis. However, the rate of valve involvement and complications is low.

58. **Answer: B. CT scan with contrast.** This patient has pyelonephritis that likely progressed to a renal or perinephric abscess, which is indicated by the persistent fever. Patients with this complication will present with symptoms typical of pyelonephritis (fevers, chills, flank pain, abdominal pain, anorexia, nausea/vomiting), but will continue to be febrile despite treatment with appropriate antibiotics. Most cases of renal/perinephric abscesses are caused by urologic pathogens (e.g., *E. coli* and other enteric gram-negative bacilli), but *Staphylococcus aureus* is also common and arrives at the kidneys by hematogenous spread. The best diagnostic test is a CT scan of the abdomen with contrast, although a renal ultrasound can also identify many

renal/perinephric abscesses. If the abscess is small (<5 cm), it can be observed with antibiotics alone; if the patient does not respond to antibiotics, or if the abscess is large (≥5 cm), both antibiotics and drainage are necessary. Antibiotic therapy should always be based on culture and sensitivity data when available. Empiric therapy for renal/perinephric abscesses is the same as for pyelonephritis and depends on susceptibility data. Options include a carbapenem, piperacillin-tazobactam, fluoroquinolone, ceftriaxone, and antistaphylococcal therapy if *S. aureus* is suspected. **(A)** The presence of WBC casts does not necessarily indicate acute interstitial nephritis or glomerulonephritis; it may also indicate an upper urinary tract infection such as pyelonephritis. Therefore, a renal biopsy is not the next step. **(C)** Failure to defervesce after treatment with antibiotics raises the concern for a complication of pyelonephritis, such as a renal or perinephric abscess, and therefore further diagnostic workup should be pursued. **(D, E)** The organism is sensitive to both antibiotics, so there is no benefit of changing antibiotics or stopping antibiotics.

59. **Answer: D. Intubation.** The patient in this vignette is experiencing an acute asthma exacerbation with worrisome symptoms/signs: wheezes with quiet respirations indicating poor air movement, use of respiratory accessory muscles, tachycardia, tachypnea, and poor oxygen saturation. In addition, the arterial blood gas shows a normal $PaCO_2$ which is worrisome; hypoxic patients should hyperventilate to maintain oxygenation, so you would expect to find hypocapnia and a respiratory alkalosis. When a patient with tachypnea to this degree has a normal $PaCO_2$, this is a sign that the patient is tiring and decompensating. Even though intubation should be avoided if possible, there is a low threshold for intubating patients that are showing signs of respiratory fatigue. **(A)** Increasing the oxygen flow rate might improve oxygenation, but the patient is likely starting to develop hypercapnic respiratory failure, which is due to inadequate ventilation. Once the patient is on a ventilator, ventilation is controlled primarily by adjusting the respiratory rate or tidal volume.

Oxygenation can be maintained by adjusting the FiO_2 and positive end-expiratory pressure (PEEP). **(B)** IV corticosteroids are used in acute exacerbations but will not take effect immediately to prevent this patient from further decompensation. **(C)** Azithromycin and other antibiotics are used in acute COPD exacerbations, not acute asthma exacerbations. **(E)** This arterial blood gas shows a normal $PaCO_2$ which is worrisome. Although nebulized albuterol is typically first-line treatment for acute asthma exacerbation, this patient is decompensating as evidenced by the arterial blood gas and intubation must be pursued next.

60. **Answer: B. Positively birefringent rhomboid-shaped crystals.** This patient has a history of parathyroid adenoma which is likely causing hypercalcemia secondary to hyperparathyroidism. Patients with hypercalcemia are at risk for developing pseudogout or CPPD, a rheumatologic disease with diverse symptoms and signs arising from the accumulation of calcium pyrophosphate dihydrate crystals in the connective tissues. It commonly presents with acute onset, painful monoarthropathy of the knee. Joint aspiration with synovial fluid analysis confirms the diagnosis, showing rhomboid-shaped crystals that are positively birefringent. **(A)** Negatively birefringent needle-shaped crystals describe *gout,* which also presents with acute onset monoarthropathy, but usually affects the first metatarsophalangeal joint of the foot. Furthermore, gout is not triggered by hypercalcemia. **(C, D)** Neutrophil predominant synovial fluid with gram-positive cocci is diagnostic of septic arthritis. This patient has no fever, making septic arthritis highly unlikely from the clinical picture alone. **(E)** Normal synovial fluid findings are not the norm in the setting of pseudogout.

61. **Answer: B. Acute retroviral syndrome.** Acute HIV infection can present in a variety of ways, but typical symptoms of the “acute retroviral syndrome” include a mononucleosis-like syndrome with fever, lymphadenopathy, headache, myalgias/arthralgias, sore throat, and a maculopapular rash. Another less sensitive but more specific finding is painful, well-demarcated mucocutaneous ulcerations.

Additional clues to the diagnosis in this case are the patient's social history (inconsistent barrier contraceptive use, IV drug use) and negative test results for other conditions on the differential diagnosis (mononucleosis due to EBV, syphilis, and other STIs, etc.). During the acute phase of HIV infection, there may be a negative screening antibody test (ELISA may take weeks to become positive) with elevated RNA viral load. A p24 antigen assay with the ELISA test has better ability to detect early infection (approximately 5 to 7 days after viral RNA is detectable), but there is still a window of time for acute HIV infection in which both ELISA and p24 antigen will be negative. **(A)** The finding of diffuse nontender lymphadenopathy is more consistent with a systemic process such as a viral infection rather than Hodgkin lymphoma, which often presents with focal or asymmetric lymphadenopathy. **(C)** Though heterophile-negative mononucleosis due to CMV is a possibility, the findings of both a maculopapular rash and mucocutaneous ulcerations make HIV more likely (both may occur in CMV infection but are less common manifestations, and GI ulcerations usually occur in the setting of immunosuppression). **(D)** Secondary syphilis is less likely to have mucocutaneous ulcerations and the screening test was negative. Although false negatives are possible with RPR and VDRL tests, the constellation of findings makes HIV infection much more likely than a false-negative syphilis test. **(E)** These clinical findings are much more severe than typical upper respiratory infection symptoms.

62. **Answer: C. Obtain a chest x-ray; if normal, start rifampin, isoniazid, and pyridoxine for 3 months.** There are a couple of important teaching points in this vignette. First, screening for TB is often performed with a PPD or an interferon gamma release assay (IGRA). In patients with close contact to a patient with active TB, a concerning chest x-ray, or who are immunosuppressed, a positive test is ≥5 mm. For those patients at high risk (healthcare workers, prison/jail residents or employees, persons experiencing homelessness, IV drug users, persons with conditions that increase risk of reactivation such as diabetes or CKD requiring dialysis, etc.), a positive test is ≥10 mm. And for all others without risk factors, a

positive test is ≥15 mm. This patient has an induration of 11 mm and is a healthcare worker, therefore she warrants further workup to differentiate active from latent TB. (Note: prior BCG vaccination rarely produces an induration >10 mm as an adult, and the CDC recommends that BCG vaccination status should not influence the workup and treatment of TB.) If the chest x-ray is negative, then the patient has latent TB and should be treated with 3 months of rifampin, isoniazid, and pyridoxine (vitamin B6, which helps to prevent isoniazid-induced neuropathy). Alternatively, other treatment options include isoniazid for 6 or 9 months, isoniazide and rifapentine for 3 months, or rifampin for 4 months. **(A)** Treatment of active TB is becoming complicated with MDR TB, however active TB is generally treated with a 4-drug regimen (rifampin, isoniazid, pyrazinamide, ethambutol) for 2 months followed up a 2-drug regimen (rifampin, isoniazid) for 4 months. **(B)** Because this patient is a healthcare worker, she should be treated for latent TB given the risk of reactivation and exposure to other patients. **(D)** A chest x-ray should be performed before starting treatment to differentiate latent from active TB. **(E)** Reassurance would only be appropriate if the PPD result was negative.

63. **Answer: A. Serum iron studies.** The patient in this question is presenting with a microcytic anemia (MCV <80 fL). The differential diagnosis of microcytic anemia can be remembered by the mnemonic "*TAILS*" (*T*halassemia, *A*nemia of chronic disease, *I*ron-deficiency anemia, *L*ead poisoning, *S*ideroblastic anemia). The most common cause of microcytic anemia is iron deficiency and the best next step is ordering iron studies: serum iron, total iron-binding capacity (TIBC), and serum ferritin. In iron-deficiency anemia, serum iron is typically low, TIBC is increased, and serum ferritin is low. After iron-deficiency anemia is confirmed, the underlying cause should be determined. **(B)** Hemoglobin electrophoresis would be useful for diagnosing thalassemia. β-Thalassemia trait usually has reduced or absent HbA, elevated levels of HbA2, and increased HbF. Clinical manifestations generally arise very early in life. **(C)** Although lead poisoning is a cause of microcytic anemia, it is uncommon and should

only be sought after iron-deficiency anemia has been ruled out. **(D)** A Coombs test would be helpful to evaluate for autoimmune hemolytic anemia, but this is not suggested by his presentation and is less common than iron deficiency anemia. **(E)** If iron deficiency is confirmed, a stool FIT test or colonoscopy should be considered later, although this patient's young age makes malignancy less likely.

64. Answer: C. Elevated lipase. The patient in this question is presenting with signs and symptoms of acute pancreatitis (epigastric abdominal pain radiating to the back, nausea, and vomiting). The vast majority of cases (80%) result from gallstones and alcohol. However, other causes of acute pancreatitis can be remembered with the mnemonic *I GET SMASHED* (Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps/Malignancy, Autoimmune, Scorpion/spider bite, Hypertriglyceridemia/hypercalcemia, ERCP, Drugs [specifically diuretics, gliptins, HIV medications, sulfonamides]). Acute pancreatitis can be diagnosed through several modalities: physical examination demonstrating epigastric pain radiating to the back, elevated amylase and lipase levels (typically 3× higher than the normal limit), and abdominal imaging (CT) showing pancreatic enlargement with heterogeneous enhancement with IV contrast. Ultrasound is also helpful in diagnosing gallstone pancreatitis by visualizing gallstones in the gallbladder. Lipase has the greatest *specificity* of all possible tests and is usually more elevated than amylase in acute pancreatitis. **(A)** Amylase can sometimes be normal in acute pancreatitis (particularly if the etiology is hypetriglyceridemia). Furthermore, amylase is not specific to the pancreas as there is not only pancreatic amylase, but also salivary amylase. **(B)** Although elevated ALT is useful in suggesting *gallstone* pancreatitis, it does not encompass all the causes of acute pancreatitis and therefore is not a specific test. **(D)** Positive fecal fat test is typically positive (>7 g/day) in *chronic* pancreatitis, however chronic pancreatitis presents with symptoms of malabsorption and is typically after multiple recurrent bouts of acute pancreatitis due to alcohol use. **(E)** Pancreatic calcifications are seen in chronic pancreatitis, not acute pancreatitis.

65. Answer: B. Thyroid-stimulating hormone (TSH) levels. The patient in this question is demonstrating clinical manifestations of hypothyroidism. In approaching the diagnosis of thyroid disorders, the first step is to order a TSH level. TSH is the *most sensitive* test to detect primary hypothyroidism and hyperthyroidism. Based on the TSH level, additional tests can be performed. **(A)** Free T4 is important in the diagnostic workup of thyroid disorders and should be the next test ordered if TSH comes back abnormal. If free T4 is increased with a decreased TSH level, this is diagnostic of primary hyperthyroidism. If free T4 is low with a high TSH level, this is primary hypothyroidism. If free T4 is decreased with a decreased TSH level, then central hypothyroidism is the diagnosis and the etiology involves the pituitary gland or the hypothalamus. Finally, if free T4 is normal with a decreased TSH, then this is subclinical hypothyroidism. **(C)** Thyroglobulin is often increased in goiter and hyperthyroidism and is also a tumor marker for thyroid cancer. It is not the best first test in working up thyroid disorders. **(D)** Radioactive iodine uptake (RAIU) scan is the next best step once primary hyperthyroidism is diagnosed (increased free T4 with decreased TSH) as it can help differentiate causes of hyperthyroidism (Graves vs. multinodular goiter vs. silent thyroiditis). **(E)** Thyroid biopsy is far too invasive of a test without a baseline TSH level.

66. Answer: A. CT scan. The suspected diagnosis here is meningitis, and a CT scan should be performed first to rule out mass effect before a lumbar puncture is performed. He has a high fever, as well as other symptoms/signs of meningitis (including the most sensitive test for meningitis: the jolt accentuation sign, in which a patient's headache intensifies after a quick head jolt). Kernig and Brudzinski signs are not sensitive, but they are fairly specific. Once a diagnosis of meningitis is suspected and a lumbar puncture needs to be performed, a CT scan should be performed in patients at high risk for cerebral herniation. Risk factors include papilledema, previous CNS disease, a seizure in that past week, immunosuppression, altered consciousness, and focal neurologic signs. **(C)** This patient has both a recent seizure and a focal neurologic sign (facial droop), and therefore a CT scan

should be performed before a lumbar puncture to assess the risk for cerebral herniation during lumbar puncture. **(B)** An MRI provides better visualization of the brain, but is costly and time-consuming. Because the purpose here is to rule out mass effect, a CT scan is the test of choice as it is much quicker. **(D)** Dexamethasone is coadministered with antibiotics if bacterial meningitis is suspected. In cases in which there is high clinical suspicion for bacterial meningitis, and a CT scan before LP will cause a delay in treatment, it is recommended to draw blood cultures and then administer empiric antibiotics and dexamethasone before LP (this is one situation where empiric antibiotics should be administered first, as mortality from untreated bacterial meningitis is high). However, dexamethasone alone is not sufficient treatment. **(E)** Empiric antiviral therapy is appropriate if HSV encephalitis is suspected. However, at this point, bacterial meningitis is more likely and the patient should undergo CT scan and LP.

67. **Answer: B. Electrolyte abnormality.** The patient in this question is presenting with anemia, low back pain, lytic lesions, increased erythrocyte sedimentation rate (ESR), and renal dysfunction, suggesting the diagnosis of multiple myeloma. A peripheral smear often shows the rouleaux formation (stacked appearance of RBCs). This patient additionally is presenting with constipation and confusion, both symptoms of hypercalcemia (>10.2 mg/dL), which is seen in about one-third of patients with multiple myeloma. The etiology of hypercalcemia in multiple myeloma is bone lysis from humoral factors released by the plasma cells. **(A)** Mechanical obstruction secondary to malignancy also can cause constipation, but the patient's signs and symptoms do not support a diagnosis of colon cancer. **(C, D, E)** Hormone level and blood gas abnormalities are typically not seen in multiple myeloma and are not associated with constipation.

68. **Answer: B. Surgery.** This patient is presenting with signs and symptoms consistent with a diagnosis of cauda equina syndrome, a serious neurologic condition in which damage to the cauda equina (a

bundle of spinal nerves originating in the conus medullaris) causes acute loss of function of the lumbar plexus. The management of this condition is urgent surgical decompression. Steroids are sometimes administered concurrently, especially if the cause of spinal cord compression is due to malignancy. **(A)** Physical therapy would not be the ideal treatment for cauda equina syndrome, which requires urgent surgical evaluation. **(C)** An x-ray of the lumbar spine would be insufficient to make the diagnosis of cauda equina syndrome (a clinical diagnosis based on history and exam) and would only delay treatment. An MRI of the lumbar spine is reasonable, but surgical consultation should be prioritized. **(D, E)** Given the finding of absent rectal tone and saddle anesthesia, conservative management with NSAIDs and bed rest should be avoided as cauda equina syndrome is a neurologic emergency.

69. **Answer: A. Aortic aneurysm.** The patient in this question is presenting with signs, symptoms, and laboratory values consistent with a diagnosis of giant-cell arteritis (GCA), also known as temporal arteritis. Symptoms can include headache, visual problems, jaw claudication, fever, and temporal scalp tenderness. GCA is a vasculitis most commonly involving large and medium arteries of the head, predominantly the branches of the external carotid artery. A decreased temporal artery pulse can be noted as well. ESR and C-reactive protein are commonly elevated. High-dose corticosteroids should be started as soon as the diagnosis is suspected (even before confirmation by temporal artery biopsy) to prevent irreversible blindness secondary to ophthalmic artery occlusion. GCA can involve branches of the aorta leading to aortic aneurysm, thus patients should have advanced imaging of the aorta (CT or MR angiography) performed. **(B)** Inflammatory bowel disease includes ulcerative colitis and Crohn disease and is not associated with GCA. **(C)** Hepatitis B is associated with polyarteritis nodosa (30% of the time), a vasculitis of medium- and small-sized arteries. **(D)** A smoking history is seen in thromboangiitis obliterans (Buerger disease), which presents with progressive inflammation and thrombosis of small and medium arteries of the hands and feet. Ulceration and gangrene are common

complications. **(E)** Alcohol has not been shown to be associated with the development of temporal arteritis.

70. **Answer: D. Vasovagal syncope.** Syncope is defined as loss of consciousness that results from cerebral hypoperfusion. The most common cause of syncope is neurocardiogenic (vasovagal) syncope, which is caused by a sudden surge of sympathetic activity that transiently increases the contractility of the left ventricle. Mechanoreceptors in the left ventricle sense this increased contractility and cause an excessive vagal response, which lowers heart rate and contractility. This transiently drops the blood pressure and causes syncope. These patients typically have symptoms of lightheadedness, nausea, and narrowing vision before losing consciousness and can usually partially brace their fall. Diagnosis is usually made based on history but can be confirmed with the tilt table test. **(A, E)** Cardiovascular causes of syncope include arrhythmias, mechanical heart disease (e.g., aortic stenosis and hypertrophic cardiomyopathy), pulmonary embolism, aortic dissection, and cardiac tamponade. Patients with sudden-onset syncope and trauma to the face (indicating an inability to brace the fall) should increase suspicion for a cardiac etiology. **(B)** Orthostatic hypotension usually occurs in the presence of hypovolemia, dysautonomia, and/or certain medications (e.g., diuretics and β-blockers). Diagnosis can be made if systolic blood pressure decreases by ≥20 mm Hg, often with associated reflex tachycardia of more than 20 beats/min when going from a sitting to a standing position, which was not seen in this patient. **(C)** Seizures technically do not meet the definition of syncope, since they are not caused by a disruption in cerebral blood flow. History that would support a seizure includes a preceding aura, tonic–clonic movements during the episode, and a postictal state (confusion with gradual improvement in neurologic function).

71. **Answer: D. Serum protein electrophoresis (SPEP).** The patient in this question is presenting with signs and symptoms consistent with a diagnosis of multiple myeloma. *CRAB* can be a useful mnemonic in diagnosing multiple myeloma: Hyper*C*alcemia, *R*enal failure, *A*nemia,

*B*one lesions (often punched out lesions in the skull). Serum and urine electrophoresis with immunofixation may reveal a monoclonal spike and is useful for confirmation of the diagnosis. **(A)** CA 15-3 is a tumor marker for breast cancer. **(B)** CEA is a tumor marker for adenocarcinomas, particularly colon (but also lung, breast, and stomach). **(C)** Alkaline phosphatase may be abnormal in multiple myeloma but is nonspecific. It would be significantly elevated in Paget disease, but Paget disease is not characterized by hypercalcemia. Furthermore, Paget disease is characterized by a *mixed* osteolytic and osteoblastic phage (where multiple myeloma is purely osteolytic). As a result, rather than showing punched out skull lesions as seen in multiple myeloma, Paget disease will show a "cotton wool" appearance due to irregular areas of sclerosis. **(E)** An abnormal bone scan may show lytic lesions in multiple myeloma, but is not diagnostic of multiple myeloma; rather it is useful in diagnosing cancer of the bone or cancers that have metastasized to the bone.

72. **Answer: D. Hypertensive emergency; rapid lowering of blood pressure with IV agents.** Hypertensive urgency, also known as asymptomatic severe hypertension, is defined as a systolic blood pressure ≥180 mm Hg and/or a diastolic blood pressure ≥120 mm Hg with no end-organ damage. Hypertensive emergency is the same definition but with the presence of end-organ damage. Many organs are acutely affected by high blood pressure, including the brain (stroke or encephalopathy), eyes (papilledema), heart (MI, aortic dissection), lungs (pulmonary edema), and kidneys (renal failure or oliguria). Within the umbrella term of hypertensive emergency, there are additional terms for specific end-organ involvement: malignant hypertension refers to hypertensive emergency in the presence of papilledema (other ophthalmologic findings include retinal exudates and hemorrhage), and malignant nephrosclerosis refers to renal damage. This patient has a hypertensive emergency with end-organ involvement including the brain (encephalopathy) and the eyes (papilledema). (**A, B, C, E**) The management of hypertensive urgency and emergency is different. In hypertensive urgency, the goal is to gradually lower the blood pressure to achieve a normal value within a

couple of days. Oral antihypertensive agents are given. This typically does not require hospital admission. Some options for oral medications include labetalol, captopril, clonidine, furosemide, and hydralazine. In hypertensive emergency, there is ongoing end-organ damage and therefore blood pressure needs to be lowered quickly. The goal in this setting is to immediately lower blood pressure using IV agents, targeting a decrease in mean arterial pressure by 10% to 20% within the first hour, and gradually by another 10% over the next 23 hours. Some options for IV medications include nitroprusside, nitroglycerin, calcium channel blockers (e.g., nicardipine), labetalol, hydralazine, fenoldopam, and phentolamine. Because adaptive mechanisms occur with chronically elevated blood pressure, rapid lowering of blood pressure is not always tolerated and can cause cerebral hypoperfusion. If this happens, the blood pressure must be lowered more gradually.

73. **Answer: C. Normal pressure hydrocephalus.** The patient in this question is presenting with dementia, urinary incontinence, and gait disturbance. This triad, often remembered by "wet, wacky, wobbly," is characteristic of normal pressure hydrocephalus (NPH). NPH is diagnosed by MRI, which will show dilated ventricles. As one would expect from the name, the opening pressure measured during lumbar puncture is normal. Treatment generally consists of repeated spinal taps to improve the symptoms (by decreasing the pressure exerted on the adjacent cortical tissue by the enlarged ventricles). **(B)** Alzheimer disease is not associated with gait problems or urinary incontinence (incontinence can develop but usually late in the clinical course). **(A)** Pseudotumor cerebri, also known as idiopathic intracranial hypertension, is associated with headaches, not memory impairment or dementia. Furthermore, it is typically seen in young women of childbearing age who are overweight. **(D)** Although this patient has a history of hypertension, it is well controlled and thus her symptoms are unlikely to be a result of vascular dementia. This type of dementia tends to be very abrupt in onset and show multiple areas of increased T2-weighted density on MRI in the periventricular regions. **(E)** Lewy

body dementia is the second most common form of dementia (after Alzheimer's) closely associated with Parkinson disease.

74. Answer: C. Amiodarone. Amiodarone is an antiarrhythmic medication that may be used for prophylaxis or treatment of serious arrhythmias, especially ventricular arrhythmias. This patient has a history of ventricular tachycardia, and therefore has an indication for amiodarone. This drug has many toxicities, and therefore when started the patient must have baseline pulmonary function tests, thyroid function tests, and liver function tests due to the toxicity involving each of these organs. Other notable side effects include blue-gray discoloration of the skin, corneal deposits, and peripheral neuropathy. This patient developed pulmonary fibrosis as a result of chronic amiodarone use. **(A, B, E)** Digoxin, lisinopril, and losartan are not associated with pulmonary fibrosis. **(D)** Bleomycin can cause pulmonary fibrosis, but it is an antineoplastic drug and the patient has no reason to be taking this medication.

75. Answer: C. Prochlorperazine. The patient in this question is likely having an acute episode of a migraine headache. Migraines are characterized by unilateral, pulsating pain that is often associated with photophobia and an aura of neurologic symptoms prior to the onset of the headache. Acute attacks can range in duration from 4 to 72 hours. Acute treatment and primary preventive treatment vary in migraine headaches. Acute attacks are best treated with intravenous antiemetic medications (prochlorperazine and metoclopramide) and/or triptans (sumatriptan). **(E)** As that this patient presents with vomiting, prochlorperazine is the best choice since it can be given in IV form, unlike sumatriptan. Sumatriptan can be given in subcutaneous form but is associated with more adverse effects. **(A, B)** Propranolol and amitriptyline are both excellent medications used for migraine *prophylaxis,* not for acute episodes. These would be appropriate to give to the patient after her acute migraine episode resolves to prevent further attacks. **(D)** Verapamil is a calcium channel blocker that is the first-line medication for cluster headache prophylaxis. However, this patient is having a migraine, not a cluster headache. Cluster headaches

typically involve pain around the eye with eye watering, nasal congestion, and swelling.

76. **Answer: C. Fractional excretion of sodium (FENa).** Acute kidney injury (AKI) is defined as an abrupt rise (within 48 hours) in serum creatinine by ≥0.3 mg/dL from baseline, a ≥50% increase in serum creatinine from baseline, or oliguria of <0.5 cc/kg/hr for >6 hours. Once AKI is recognized, the next step in diagnosis is determining whether the etiology is prerenal, intrinsic renal, or postrenal. These terms reflect the perceived sight of pathology; prerenal AKI is caused by decreased blood flow to the kidneys, intrinsic renal AKI is caused by direct damage to the kidney parenchyma (i.e., to the renal vasculature, tubules/interstitium, or glomeruli), and postrenal AKI is caused by an obstruction in the urinary tract leading away from the kidneys. The patient in this question is hypovolemic (tachycardia and dry mucus membranes). In response to hypovolemia, the renal arterioles vasoconstrict, decreasing blood flow to the kidneys and decreasing the glomerular filtration rate (GFR). Prerenal AKI is a result of ischemia from poor perfusion, however it can progress to acute tubular necrosis (ATN), which is a form of intrinsic renal AKI. Besides hypovolemia, her daily NSAID may also be contributing to the AKI since NSAIDs cause renal vasoconstriction. One of the best tests for differentiating between prerenal AKI and ATN is the FENa. In prerenal AKI, sodium is reabsorbed in an attempt to maintain circulating blood volume, and therefore there will be little sodium in the urine. **(B)** Although this is often reflected by the urine sodium, this value is affected by renal water handling and urine output. FENa is a better test, since it only measures the fraction of sodium excretion and is not affected by urine output. In general, low FENa values indicate prerenal AKI and high values indicate intrinsic renal AKI (tubular damage leads to salt wasting). The FENa will be <1% in prerenal AKI and >2% in ATN. (Note: FENa should not be used if the patient is taking diuretics, but the fractional excretion of urea may be used instead.) **(A)** A urine dipstick is a helpful screening tool for things such as proteinuria or infection, but it will not help to differentiate between prerenal and intrinsic renal AKI. **(D)** A renal ultrasound

would be helpful in excluding postrenal AKI, which is not suspected in this case. **(E)** Urine eosinophils are of limited diagnostic utility. They were thought to be associated with acute interstitial nephritis (AIN), but are neither sensitive nor specific for this diagnosis.

77. Answer: B. Aortic dissection. The most important risk factor for aortic dissection in the general population is hypertension, however there is a high incidence in patients with connective tissue disease (e.g., Marfan and Ehlers–Danlos syndromes). Sharp chest pain radiating to the back is the first clue to this diagnosis. Other symptoms may occur based on which arteries are occluded by the dissected flap. Finally, a widened mediastinum is seen on chest x-ray. Other potential manifestations not seen in this patient are cardiac tamponade and Horner syndrome (from compression of the superior cervical ganglion). Dissections involving the proximal aorta require immediate surgical intervention. **(A, C, D)** All of these diagnoses are a potential result of the patient's aortic dissection, but are not the underlying (primary) diagnosis. Acute coronary syndromes (ACS) may occur during an aortic dissection as a result of involvement of one or more coronary arteries, and stroke can occur with involvement of the carotid arteries. Aortic regurgitation is common in patients with Marfan syndrome, and this can also occur as a result of a dissection in the ascending aorta. In either situation, it is not the primary diagnosis. **(E)** Hypertensive emergency requires a systolic blood pressure ≥180 mm Hg and/or a diastolic blood pressure ≥120 mm Hg in the presence of end-organ damage.

78. Answer: B. *Salmonella*. Patients with sickle cell disease often have functional asplenism from infarction. This often results in impaired immunologic response to encapsulated organisms, such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis.* Furthermore, they are more prone to invasive *Salmonella* infections which, when localized, can result in osteomyelitis. In addition to treatment with antibiotics here, this patient should immediately be treated with oxygen, aggressive

hydration, and analgesics. **(A, C, D, E)** These organisms do not cause osteomyelitis in sickle cell patients.

79. Answer: D. Hot nodule on RAIU. Thyroid nodules are fairly common with a 5% to 10% prevalence. Approximately 5% of thyroid nodules are malignant. **(A, B, C, E)** Factors associated with malignancy include history of radiation to the neck, male sex, hard and immobile mass, age greater than 70 years, worrisome ultrasound findings such as irregular borders and microcalcifications, cervical lymphadenopathy, and cold nodule on RAIU. Cold nodules are nonfunctional and do not absorb the radioiodine. Hot nodules, on the other hand, are autonomous (toxic) and readily absorb the radioiodine. However, hot nodules are benign and not associated with malignancy.

80. Answer: D. Dual-energy x-ray absorptiometry (DEXA). Risk factors for osteoporosis include smoking, family history, low body weight, excessive alcohol use, and secondary organic causes such as premature menopause, among others. Regardless of symptoms, the USPSTF recommends a one-time screening for osteoporosis in *all* women aged 65 years or older with DEXA scan of the spine and hips. A bone density with T-score <2.5 standard deviations below the mean is associated with osteoporosis and a T-score between 1 and 2.5 standard deviations below the mean is associated with osteopenia. **(A)** The patient had a normal mammogram the year before. Mammograms should be performed every 2 years in her age group. **(B)** The patient had a colonoscopy 6 years ago that was normal. She is due for another colonoscopy in 4 years (reaching the 10-year mark after her previous one). **(C)** Calcium and phosphorus levels are normal in patients with osteoporosis and have no value in screening for the condition. **(E)** There is no significant smoking history or clinical suspicion here for lung cancer, so a CT scan of the chest is not warranted.

81. Answer: B. Joint aspiration with synovial fluid analysis. This patient is presenting with signs and symptoms consistent with an acute gout attack. The patient's alcohol use lends credence to the history of gouty arthritis. Furthermore, the patient is presenting with

acute right knee pain, swelling, and low-grade fever, all confirming the likely diagnosis of gout. As septic arthritis and pseudogout can present similarly to gout, it is imperative to first perform joint aspiration and synovial fluid analysis. Synovial fluid analysis of gout will demonstrate a leukocyte count of 2,000 to 50,000/mm^3 and negatively birefringent needle-shaped crystals with a negative Gram stain and negative culture. **(A)** Indomethacin (an NSAID) is very helpful in treating acute gout. Nonetheless, the diagnosis of gout must first be confirmed before administering indomethacin especially with its side-effect profile. **(C)** Uric acid levels can be elevated in gout, but may also be low or normal during an acute flare (elevated uric acid is the underlying cause of the clinical manifestations). **(D)** An x-ray of the knee is not as specific as synovial fluid analysis for diagnosing gout.

82. **Answer: C. Empiric 8-week trial with proton pump inhibitor (PPI).** The patient in this question is presenting with dyspepsia (characterized by epigastric pain and early satiety). Dyspepsia is a common presentation, and only a minority of patients are diagnosed with an underlying etiology contributing to the dyspepsia. The most common etiologies of dyspepsia are GERD, NSAIDs, peptic ulcer disease (PUD), and malignancy. **(D)** Importantly, if a patient presents with any "alarm symptoms" such as unexplained weight loss, persistent vomiting, blood loss or unexplained iron deficiency anemia, dysphagia, odynophagia, lymphadenopathy, or family history of gastrointestinal cancer, then they should undergo an upper GI endoscopy to evaluate for malignancy. In patients without the "alarm symptoms," current recommendations are to test for *Helicobacter pylori* in regions where there is a high prevalence of the bacteria and begin treatment with a PPI. In regions where there is a low prevalence of *H. pylori,* some physicians will treat empirically with a PPI. The most important thing to note here is that patients who have persistent symptoms with either of these treatment options after 4 to 8 weeks should undergo endoscopy. **(A)** Antacids have not alleviated this patient's symptoms and therefore are not the correct answer here. **(B)** Barium swallow evaluation is not helpful in diagnosing the etiology

of dyspepsia. **(E)** This patient is symptomatic and clearly not responding to over-the-counter antacids. Observation is inappropriate.

83. Answer: E. Etiologies include infection and polypharmacy. This patient is presenting with signs and symptoms consistent with a diagnosis of delirium, which has several etiologies including infection, surgery, trauma, or polypharmacy side effects. Acute onset of symptoms, fluctuating level of consciousness, and presence of visual hallucinations favor a diagnosis of delirium over dementia. In addition, sleep–wake cycle disturbance is a prominent feature of delirium. **(D)** Delirium is reversible, while dementia, by contrast, is often irreversible. Clinically, patients with dementia show gradual decline in cognition with preserved level of consciousness. Reversible causes of delirium should be considered, including metabolic disorders, infections, medications, normal pressure hydrocephalus, nutritional deficiencies, or thyroid dysfunction, which may be potentially reversible causes of dementia-like symptoms. Delirium occurs in up to 20% of acute hospital inpatients and up to 60% of surgical patients in the perioperative period. Identifying and treating the cause of delirium is critical. **(A)** Anticholinergic medications will *worsen* delirium. **(B)** Neurofibrillary tangles and β-amyloid plaques seen on pathology are consistent with Alzheimer dementia, not delirium. **(C)** If long-term memory is intact, but short-term memory is affected, then this is more consistent with dementia.

84. Answer: B. Gallstone obstruction in the cystic duct. The patient in this question is presenting with acute cholecystitis. She is presenting with fever, right upper quadrant pain after a fatty meal that radiates to the right scapula, and positive Murphy sign (pain on palpation in the right upper quadrant with cessation of inspiration). Her history of biliary colic further supports this diagnosis. Additional nonspecific findings include vomiting, leukocytosis, and mild elevation in transaminases. Acute cholecystitis usually arises from gallstone formation that obstructs the cystic duct. The symptoms occur after eating a fatty meal because the fat stimulates gallbladder contraction, and in the presence of cystic duct obstruction, this leads to colicky

pain. Infection results from stasis that contributes to bacterial growth in the gallbladder. **(D)** Importantly, alkaline phosphatase is *not* elevated in this patient with acute cholecystitis. Assume if laboratories are not shown, they are normal. If it were elevated (in addition to total bilirubin and direct bilirubin), this might indicate common bile duct obstruction in the setting of jaundice (choledocolithiasis). **(A)** Alcoholic hepatitis does not present with this constellation of symptoms. **(C)** Similar to common bile duct obstruction, obstruction from a carcinoma of the head of the pancreas would cause severely elevated alkaline phosphatase levels and would usually present with weight loss and painless jaundice. **(E)** Pancreatitis should definitely be ruled out with a serum lipase, but pain typically is only epigastric in nature and radiates to the back.

85. **Answer: C. Amitriptyline.** The patient in this question is presenting with signs and symptoms consistent with a diagnosis of fibromyalgia (FM). FM is more common in adult women and is characterized by chronic widespread pain and allodynia (a heightened and painful response to pressure). Physical examination is typically normal except for point muscle tenderness in several areas including the mid trapezius, lateral epicondyle, and greater trochanter, among others. Of note, FM has no laboratory findings that are diagnostic of the condition. The first-line treatment for FM is patient education, aerobic exercise, and good sleep hygiene. This patient has clearly attempted those recommendations based on the history she provides, so the first-line *medication* is a tricyclic antidepressant (TCA) such as amitriptyline. Several other drugs (pregabalin and duloxetine) can be attempted if TCAs fail to alleviate the patient's symptoms. **(A, B, E)** Corticosteroids and NSAIDs are useful in treating *inflammatory* conditions, but FM is not an inflammatory condition (not associated with elevated inflammatory markers such as ESR). **(D)** Colchicine is useful in treating gout, not FM.

86. **Answer: B. Administration of fluids.** This is a common question on the USMLE that emphasizes the importance of airway, breathing, and circulation (ABCs) in the management of patients (regardless of the

underlying disorder). This patient presents with hypotension and delayed capillary refill, indicating that there is compromise of his circulation. The best next step in management of circulatory compromise (in this case from an upper GI bleed) is fluid resuscitation. Blood transfusion should also be done, but crystalloid fluids can be obtained much faster than blood products so they should be prioritized first. After the patient is hemodynamically stable, treatment for the actual underlying condition can be initiated. **(A, C, D)** All these answer choices address the underlying cause of the upper GI bleeding (likely variceal bleeding); however, the patient must be stabilized before these modalities are pursued. **(E)** This is a life-threatening condition and reassurance is inappropriate.

87. **Answer: E. CT scan of abdomen and pelvis.** The patient in this question is presenting with signs and symptoms concerning for a small bowel obstruction (SBO). The typical constellation of symptoms includes abdominal pain, vomiting, obstipation, abdominal distention, and diffuse tenderness. A mild leukocytosis is often found in an SBO. The best diagnostic test is a CT scan of the abdomen and pelvis because it can evaluate the severity of obstruction, location of a transition point, and look for any potential complications. Treatment involves supportive care, bowel rest, and decompression with a nasogastric tube. Surgery is reserved for those patients who fail to improve with the aforementioned treatments and/or develop findings consistent with strangulation. **(A, B, C, D)** These options are not the best initial test in diagnosing an SBO. Ultrasound is a poor imaging modality for bowel obstruction as any bowel gas will obscure the view.

88. **Answer: B. Nephrolithiasis.** This patient is presenting with the typical symptoms of a kidney stone. Patients with Crohn disease are at risk of developing calcium oxalate stones due to increased absorption of oxalate in the GI tract (and therefore increased oxaluria), which has two causes. First, malabsorption of bile salts and GI tract inflammation increase mucosal permeability. Second, fatty acids (also a result of malabsorption) bind intestinal calcium, and so less calcium

is available to bind and trap intestinal oxalate. This causes an increase in free oxalate that can be absorbed, eventually making it back to the kidneys to be excreted. Calcium stones are the most common type of kidney stones, and patients with these stones are encouraged to increase their dietary intake of calcium (in order to decrease oxalate absorption in the GI tract). Ammonium magnesium phosphate (struvite) stones are caused by urinary tract infections with urease-positive organisms (e.g., *Proteus, Klebsiella*) and can form staghorn calculi. Uric acid stones are associated with hyperuricemia (e.g., leukemia, gout). Cystine stones are seen in the genetic disease cystinuria and are treated by alkalinizing the urine with acetazolamide. **(A)** Pyelonephritis would also produce flank pain, but unlike nephrolithiasis it would also produce fever, leukocytosis, and a urine dipstick showing inflammation (e.g., positive nitrites, positive leukocyte esterase). **(C)** Appendicitis is important to consider in any young patient with abdominal pain, however it would be unusual for appendicitis to cause hematuria. **(D)** Ectopic pregnancies can mimic the pain of a kidney stone, but this diagnosis is unlikely given the negative pregnancy test. **(E)** This would be an unusual presentation of abdominal pain seen in pancreatitis, which is usually epigastric and radiating to the back.

89. **Answer: C. Hyperventilation secondary to anxiety.** According to the ABG, this patient has an acute respiratory alkalosis (caused by loss of CO_2 which is balanced by increased excretion of HCO_3). Respiratory alkalosis can only be caused by an increase in ventilation (commonly caused by high altitudes or sympathetic stimulation like anxiety or pain). **(A)** Accumulation of unmeasured anions due to hepatic metabolism of alcohol would cause an anion gap metabolic acidosis (*low* pH with *low* HCO_3 and *low* CO_2 and an increased gap, calculated by subtracting [$Cl^- + HCO_3^-$] from Na^+). **(B)** Vomiting causes a *metabolic* alkalosis from loss of acid and chloride. Metabolic alkalosis is characterized by *high* pH, *high* HCO_3, and *high* CO_2 (respiratory compensation by hypoventilating). **(D)** Diuretics are associated with a *metabolic* alkalosis from volume contraction. **(E)**

Hypoventilation causes a *low* pH from CO_2 retention. This will cause a *respiratory* acidosis, not alkalosis as seen with this patient.

90. **Answer: C. Lactulose.** This patient is presenting with signs and symptoms of cirrhosis (ascites, spider angiomata) and hepatic encephalopathy (altered mental status and asterixis). In hepatic encephalopathy, the liver is unable to convert ammonia into urea and it therefore accumulates, in addition to other toxins the liver is unable to clear. It is often precipitated by illness, infection, or gastrointestinal bleed. Serum ammonia levels have no utility in the diagnosis of hepatic encephalopathy, as ammonia levels may be low, normal, or elevated and HE is a clinical diagnosis. Treatment involves treating the precipitant and administering therapies to increase gut excretion of ammonia. Lactulose, a nonabsorbable disaccharide, is used because bacteria in the gut metabolize it into acidic compounds (lactic acid, acetic acid) that permit the *absorbable* ammonia to be converted into the *nonabsorbable* ammonium, thereby enabling excretion from the body. **(A)** Furosemide would improve the ascites and volume status in a cirrhotic patient, but is not helpful in the management of hepatic encephalopathy. **(B)** Thiamine is useful in the treatment of *Wernicke encephalopathy,* another form of encephalopathy characterized by altered mental status, ataxia, and nystagmus and is associated with thiamine deficiency. Of note, asterixis is not a common feature in Wernicke encephalopathy. **(D, E)** Morphine and hydromorphone are opioids that are not the treatment for hepatic encephalopathy. Moreover, many opioids have altered metabolism in cirrhosis so should be used with caution.

91. **Answer: B. Acetaminophen.** This patient is obese, greater than 40 years of age, and is presenting with bilateral knee and back pain. The fact that the pain is worsened with activity and relieved by rest suggests that it is most likely secondary to osteoarthritis (OA). If she reported morning stiffness lasting greater than 30 minutes and had systemic symptoms, rheumatoid arthritis would have been the likely diagnosis. OA is a *noninflammatory* arthritis that results in eroding cartilage in the intra-articular joints. This causes joint crepitus (a

“grating” or popping sound) that occurs when the surfaces of the joint grind against each other. Although the diagnosis is usually made clinically, the typical changes seen on x-ray include joint space narrowing, subchondral sclerosis (increased bone formation around the joint), subchondral cyst formation, and osteophytes. Acetaminophen is the first-line treatment for mild-to-moderate OA. It is just as efficacious as NSAIDs in alleviating the pain in OA with considerably fewer side effects. **(A)** Intra-articular corticosteroid injections lead to short-term pain relief that lasts up to a few months. This should not be the initial treatment in OA. **(C)** Naproxen is an NSAID and although NSAIDs have been shown to be efficacious in the treatment of OA, their side-effect profile consists of gastrointestinal and renal consequences that make them second-line treatments. **(D)** Allopurinol is used in the prophylactic treatment of gout. It acts via inhibition of xanthine oxidase which decreases production of uric acid. It is not used in the treatment of OA. **(E)** This patient is clearly in pain and would benefit from medication, so observation is inappropriate.

92. Answer: D. Vitamin B_{12} deficiency. The patient in this question likely has cobalamin (vitamin B_{12}) deficiency. This results in a megaloblastic anemia. Long-term consequences of vitamin B_{12} deficiency include peripheral neuropathy and posterior column defects from abnormal myelin synthesis. Importantly, folic acid deficiency is another cause of macrocytic anemia and treatment with folic acid can improve the actual *anemia* of vitamin B_{12} deficiency since both folate and vitamin B_{12} are involved in the conversion of homocysteine to methionine. However, neurologic symptoms can be worsened in vitamin B_{12} deficiency with the treatment of folic acid since vitamin B_{12} is used in other biologic processes as well. As a result, it is critical to rule out vitamin B_{12} deficiency before initiating folic acid. Vitamin B_{12} deficiency results from inadequate vitamin B_{12} intake (diet lacking in animal products) and autoimmune gastritis. The loss of gastric parietal cells secondary to autoimmune gastritis causes

intrinsic factor deficiency (which is necessary for vitamin B_{12} absorption in the terminal ileum). **(A)** The patient's underlying disorder is vitamin B_{12} deficiency and no amount of folic acid supplementation will improve his neurologic symptoms. **(B)** Iron deficiency is a microcytic anemia (MCV <80 fL) and is not associated with peripheral neuropathy. **(C, E)** Although glucose intolerance commonly causes peripheral neuropathy, this patient does not have a history that suggests diabetes.

93. **Answer: A. Amlodipine.** Amlodipine is a calcium channel blocker that is often used as an antihypertensive agent. It has a high incidence of peripheral edema as a side effect. **(B)** Metoprolol is a selective β_1-blocker used in hypertension, heart failure, and rate control for tachyarrhythmias such as atrial fibrillation. It can cause bradycardia and hypotension, but avoids some of the adverse effects of nonselective β-blockers (e.g., bronchospasm). It rarely causes peripheral edema. **(C)** Hydrochlorothiazide blocks the Na-Cl channel in the distal convoluted tubule, leading to sodium and water excretion. It is used as an antihypertensive agent, and can cause orthostatic hypotension, hypercalcemia, hypokalemia, hyperlipidemia, and hyperglycemia. **(D)** Metformin is a biguanide drug used in diabetes and acts by decreasing hepatic glucose secretion and increasing insulin sensitivity. It causes GI symptoms, vitamin B_{12} deficiency, and, rarely, lactic acidosis in patients with significant renal failure. **(E)** Glipizide is a sulfonylurea antidiabetic drug. It blocks potassium channels in islet cells of the pancreas, leading to increased insulin release that can result in hypoglycemia.

94. **Answer: A. Factitious hypoglycemia from surreptitious injection of insulin.** The patient in this question is presenting with clinical symptoms and laboratory findings consistent with surreptitious injection of insulin (elevated insulin, decreased glucose, and decreased C-peptide). **(B)** Since this patient presents with a decreased C-peptide level, this is not consistent with an *endogenous* source of insulin since pancreatic β-cells produce proinsulin (which breaks

down into insulin and C-peptide). Therefore, insulinoma is not the diagnosis since there are decreased levels of C-peptide in this patient. Note that surreptitious sulfonylurea use will also produce elevated insulin and C-peptide levels (similar to insulinoma) since this drug essentially stimulates proinsulin secretion. That is why it is critical to order a urine sulfonylurea level, which is undetectable in this patient. **(C, D)** Somatization disorder and glucagonoma do not produce hypoglycemia. **(E)** Dehydration cannot explain the severe hypoglycemia seen in this patient.

95. **Answer: D. Ciprofloxacin.** One reported adverse reaction of fluoroquinolone antibiotics is tendinopathy, and the Achilles tendon is most often affected. Fluoroquinolones can also cause GI upset, *Clostridium difficile* colitis, dizziness, rash, and a prolonged QT interval, among many other issues. **(A)** Trimethoprim-sulfamethoxazole may cause Stevens–Johnson syndrome, leukopenia, hyperkalemia, hypoglycemia, and hepatitis. **(B)** Metronidazole can cause GI upset and peripheral neuropathy. **(C)** Tobramycin and other aminoglycosides may cause renal failure and ototoxicity. **(E)** Azithromycin and other macrolides can cause a prolonged QT interval and hepatitis.

96. **Answer: B. Thyroid-stimulating hormone (TSH) levels.** The patient in this question is demonstrating clinical manifestations of hyperthyroidism. In approaching the diagnosis of thyroid disorders, the first step is to order a TSH level. TSH is the *most sensitive* test to detect primary hypothyroidism and hyperthyroidism. Based on the TSH level, additional tests can be performed. **(A)** Free T4 is important in the diagnostic workup of thyroid disorders and should be the next test ordered if TSH comes back abnormal. If free T4 is increased with a decreased TSH level, this is diagnostic of primary hyperthyroidism. If free T4 is decreased with a decreased TSH level, then central hypothyroidism is the diagnosis and the etiology involves the pituitary gland or the hypothalamus. Finally, if free T4 is normal with a decreased TSH, then this is subclinical hypothyroidism. **(C)** Thyroglobulin is often increased in goiter and hyperthyroidism and is

also a tumor marker for thyroid cancer. It is not the best first test in working up thyroid disorders. **(D)** Radioactive iodine uptake (RAIU) scan is the next best step once primary hyperthyroidism is diagnosed (increased free T4 with decreased TSH) as it can help differentiate causes of hyperthyroidism (Graves vs. multinodular goiter vs. silent thyroiditis). **(E)** A fine-needle aspiration (FNA) biopsy is far too invasive of a test without having basic laboratory values.

97. **Answer: D. Reassurance.** This patient demonstrates immunity to hepatitis B (positive for HBsAb) and therefore reassurance should be offered. Immunity to hepatitis B occurs when anti–hepatitis B surface antibodies (HBsAbs) develop against the recombinant hepatitis B surface antigen. Given the patient's documented hepatitis B vaccination and positive titers for HBsAb, reassurance is appropriate. **(A, C)** If the patient had unknown vaccination history, she should receive *both* HBIG (passive immunity) and hepatitis B vaccine (active immunity). **(B)** The patient has documentation already revealing positivity for HBsAb. Therefore, a hepatitis B panel is unnecessary.

98. **Answer: B. Tearing of the bridging veins.** This patient is suffering from a subdural hematoma, which is caused by blunt trauma that tears the bridging veins, which connect the cortical superficial veins to the sagittal sinus in the dura. This blood will *slowly* extravasate into the subdural space, which is why this patient's fall was recorded 4 days prior to admission. Epidural hematomas, on the other hand, become immediately symptomatic (although the classic description of epidural hematomas is that of a "lucid" phase followed by rapid decline). Subdural hematomas manifest symptomatically with headache and gradual confusion and loss of consciousness. Of note, subdural hematomas are much more common in elderly patients and alcoholic patients (brain atrophy and fragility of vasculature). Radiologic findings of a subdural hematoma include a white crescent on noncontrast CT of the head. Also, a midline shift is commonly appreciated. Treatment is neurosurgical hematoma evacuation. **(A)** Tearing of the middle meningeal artery is the underlying cause of most epidural hematomas. **(C)** Ruptured aneurysm is the underlying

cause of a subarachnoid hemorrhage. **(D)** In addition to the radiologic evidence, this particular patient does not have a history of hypertension and therefore hypertensive hemorrhage is not the right answer. **(E)** Alzheimer disease would not present with this acute presentation. This patient clearly endorses trauma making a hematoma much more likely than underlying dementia.

99. **Answer: D. Severe sepsis.** This patient has severe sepsis secondary to pneumonia. It is important to know the definitions related to the topic of sepsis. Systemic inflammatory response syndrome (SIRS) is defined by 2 or more of the following: (1) temperature >38°C or <36°C; (2) a heart rate >90/min; (3) a respiratory rate >20/min or a $PaCO_2$ <32 mm Hg; and (4) a serum leukocyte count >12,000/mm^3 or <4,000/mm^3 or >10% bands. The 2016 Third International Consensus updated the definition of sepsis to be a qSOFA score of 2 or more (qSOFA includes respiratory rate of 22 or higher, altered mental status, or systolic blood pressure 100 mm Hg or less). Despite these guidelines, many providers still use the SIRS definition of sepsis and it is thus still important to know the previous definition. **(C)** When there is a suspected source of infection, the definition becomes sepsis. Severe sepsis is the definition for sepsis with end-organ dysfunction, signified by hypotension or hypoperfusion (oliguria, elevated serum lactate, etc.). Septic shock is severe sepsis that does not respond to adequate fluid resuscitation. This patient meets SIRS criteria with a suspected source of infection (pneumonia) and hypotension; **(E)** IV fluids have not been administered yet, so the definition of septic shock is not met. Septic shock is one type of distributive shock, which is characterized by hypotension with flat neck veins and warm extremities (low systemic vascular resistance). **(A, B)** Both cardiogenic shock and pulmonary embolism (a type of obstructive shock) are less likely by the clinical findings and patient's volume status on examination (flat JVP). Lastly, hypovolemic shock would present with flat neck veins and *cool* extremities, since systemic vascular resistance increases in an attempt to maintain blood pressure.

100. Answer: A. Place the patient in a semi-recumbent position. Mechanical ventilation is the biggest risk factor for developing HAP, and the risk can be decreased with certain measures. Patient should be placed in a semi-recumbent position (head of the bed elevated 30 to 45 degrees) to prevent aspiration events. **(B)** Daily attempts to wean a patient from the ventilator should be performed to minimize the duration of mechanical ventilation. **(C)** Measuring daily gastric residual volumes for patients on enteral feeds has been a standard practice, but studies show that measurement of gastric volumes does not correlate well with the risk of aspiration. **(D)** Omeprazole and other agents that increase the pH of gastric contents have been shown to increase the rate of HAP. They should be avoided if possible. **(E)** Endotracheal suctioning of subglottic secretions reduces the risk of VAP. Other important preventive measures include following proper hand hygiene protocols, avoiding gastric overdistention, and using orotracheal intubation rather than nasotracheal intubation.

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